EVALUATING THE MANAGEMENT OF CHRONIC LIMB THREATENING ISCHAEMIA DUE TO FEMORO-POPLITEAL DISEASE

By

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DEDICATION

This work is dedicated to Samantha Rowley-Meecham, my wife, for her never-ending support and encouragement. Her love and patience have never wavered even during the difficult hours of the night looking after our child, while I have been absent working for the benefit of patients with vascular disease or completing this thesis.

To Wyn, I love you with all of my heart, and hope that this thesis will be encouragement for you to find your place in the world and excel!

Thank you!

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ABSTRACT

Introduction

Peripheral arterial disease is an increasing global health problem, particularly in low and middle-income countries. Traditionally the primary cause was smoking, as smoking rates decrease and life expectancy increases, Diabetes Mellitus and renal failure are becoming more common causes. Little evidence exists to guide the treatment of chronic limb threatening ischaemia (CLTI). Best medical therapy (antiplatelet, statin, hypertensive therapy and smoking cessation) is essential to reduce the risk of secondary cardiovascular events. When it comes to revascularisation, there are now two multicentre randomised controlled trials comparing bypass surgery or endovascular intervention for infra-inguinal peripheral arterial disease; the BASIL trial and BEST-CLI. Both have reported superior outcomes for vein bypass compared to endovascular intervention and advocate a bypass surgery first approach in infra-inguinal CLTI. Bypass with synthetic conduit (PTFE or Dacron) should only be offered as a last resort. The aim of this thesis is to analyse the current trends in revascularising patients with femoro-popliteal induced CLTI, and whether these treatments have resulted in better outcomes for patients.

Methods

The BASIL trial cohort was used as a baseline for comparison. The contemporary series of patients were gathered from one large University Hospital trust (HEFT). Patients undergoing primary femoro-popliteal revascularisation (bypass surgery or angioplasty) between 2009-2014 were included. Statistical analysis was performed using SAS v9.5 and SPSS v24.

Results

Re-analysis of the cohort of patients in the BASIL trial undergoing femoro-popliteal intervention (approx. 75%) yielded very similar results to that of the whole trial cohort. Those patients who underwent secondary bypass surgery after a failed endovascular intervention did significantly worse than those who underwent primary bypass, indicating that endovascular intervention is not the free shot that is so often claimed. In terms of contemporary practise, those patients being treated either by FP endo or Bypass surgery have far worse outcomes now compared to that seen in the BASIL trial (AFS and OS) despite better technical success and better rates of medical therapy. Finally, the new Global Limb Anatomy Stage System (GLASS) accurately predicts technical success of endovascular intervention and likelihood of poorer limb outcomes as grade increases in this contemporary cohort.

Conclusion

Open surgical bypass for femoro-popliteal disease was superior to endovascular intervention when BASIL was conducted. Contemporary outcomes after femoro-popliteal revascularisation, with an endovascular first strategy, are worse than that observed in the BASIL trial.

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

PAD	-	Peripheral Arterial Disease
APAD	-	Asymptomatic Peripheral Arterial Disease
IC	-	Intermittent Claudication
CLTI	-	Chronic Limb Threatening Ischaemia
UK	-	United Kingdom
USA	-	United States of America
DM	-	Diabetes Mellitus
ESRF	-	End Stage Renal Failure
GVG	-	Global Vascular Guidelines
ABPI	-	Ankle Brachial Pressure Index
TBPI	-	Toe Brachial Pressure Index
AFS	-	Amputation Free Survival
OS	-	Overall Survival
LS	-	Limb Salvage
FFR	-	Freedom from re-intervention
MALE	-	Major Adverse Limb
MALE-S	-	Major Adverse Limb Event free Survival
MACE	-	Major Adverse Cardiovascular Event
MLLA	-	Major Lower Limb Amputation (MLLA)
BKA	-	Below Knee Amputation
TKA	-	Through Knee Amputation
AKA	-	Above Knee Amputation
BASIL	-	Bypass versus Angioplasty in Severe Ischaemia of the Leg
RCT	-	Randomised Controlled Trial
BK-pop	-	Below-Knee Popliteal Artery

OSB	-	Open Surgical Bypass
DCB	-	Drug Coated Balloon
DES	-	Drug Eluting Stent
BEST-CLI	-	Best Surgery or Endovascular Therapy for CLTI
SWEDEPAD	-	Swedish Drug Elution trial in Peripheral Arterial Disease
NIHR-HTA	-	National Institute for Health Research Health Technology Assessment Programme
PBA	-	Plain Balloon Angioplasty
BMS	-	Bare Metal Stent
FP	-	Femoro-popliteal
IP	-	Infra-popliteal
VB	-	Vein Bypass
NICE	-	National Institute of Clinical Excellence
NHS	-	National Health Service
CG 147	-	Clinical Guideline 147
BMT	-	Best Medical Therapy
BP	-	Blood Pressure
BASIL-2	-	Bypass versus Angioplasty in Severe Ischaemia of the Leg – 2
BASIL-3	-	BAlloon versus Stenting in severe Ischaemia of the Leg-3 trial
HRQL	-	Health Related Quality of Life
NIH	-	National Institute of Health
NHLBI	-	National Heart, Lung and Blood Institute
GSV	-	Great Saphenous Vein
BET	-	Best Endovascular Therapy
SVS	-	Society for Vascular Surgery of North America
ESVS	-	European Society of Vascular Surgery
WFVS	-	World Federations of Vascular Surgery

JVS	-	Journal of Vascular Surgery
EJVES	-	European Journal of Vascular and Endovascular Surgery
GLASS	-	Global Limb Anatomic Staging System
TAP	-	Target Artery Path
WIfI	-	Wound, Ischaemia and foot Infection
PLAN	-	Patient risk estimation, limb staging, anatomic pattern of disease, no option anatomy
EBR	-	Evidence Based Revascularisation
GRADE	-	Grading of Recommendations, Assessment, Development and Evaluation
KG	-	Kilogram
CM	-	Centimetre
DP	-	Dorsalis Pedis
PT	-	Posterior Tibial]
AP	-	Ankle Pressure
PEDIS	-	Perfusion, Extent, Depth, Infection, and Sensation
DUS	-	Duplex Ultrasound
US	-	Ultrasound
CTA	-	Computed Tomography Angiography
CT	-	Computed Tomography
MRA	-	Magnetic Resonance Angiography
AT	-	Anterior Tibial Artery
PP	-	Peroneal Artery
DSA	-	Digital Subtraction Angiography
ITS	-	Immediate Technical Success

CVD	-	Cardiovascular Disease
OD	-	Once Daily
DOAC	-	Direct Oral Anticoagulant
OR	-	Odds Ratio
RR	-	Relative Risk
ACEi	-	Angiotensin Converting Enzyme inhibitor
T2DM	-	Type 2 Diabetes Mellitus
eGFR	-	estimated Glomerular Filtration Rate
MI	-	Myocardial Infarction
ET	-	Endovascular Therapy
CTO	-	Chronic Total Occlusion
TLR	-	Target Lesion Restenosis
BR	-	Binary Restenosis
PTFE	-	Polytetrafluoroethylene
AK-pop	-	Above Knee popliteal artery
NCEPOD	-	National Confidential Enquiry into Patients Outcomes and Deaths
HQIP	-	Health Quality Improvement Partnership
COVID-19	-	Severe Acute Respiratory Syndrome CoronaVirus Disease – 2
SARS	-	Severe Acute Respiratpry Syndrome
NVR	-	National Vascular Registry
HEFT	-	Heart of England Foundation Trust
SynB	-	Synthetic Bypass
HTN	-	Hypertension
FF-MALE	-	Freedom From Major Adverse Limb Event

ONS	-	Office of National Statistics
COPD	-	Chronic Obstructive Pulmonary Disease
SD	-	Standard Deviation
IQR	-	Inter-Quartile Range
ESC	-	European Society of Cardiology
PB	-	Primary Bypass
SB	-	Secondary Bypass
ITT	-	Intention To Treat
CRF	-	Case Report Forms
IDDM	-	Insulin Dependent Diabetes Mellitus
NIDDM	-	Non-Insulin Dependent Diabetes Mellitus
TIA	-	Transient Ischaemic Attack
LRTI	-	Lower Respiratory Tract Infection
UTI	-	Urinary Tract Infection
SFA	-	Superficial Femoral Artery
POP	-	Popliteal Artery
TPT	-	Tibio-Peroneal Trunk
FP-PBA	-	Femoro-Popliteal Plain Balloon Angioplasty
CS	-	Contemporary Series
B1	-	BASIL-1
HR	-	Hazard ratio
PCS	-	Prospective Cohort Series
LBP	-	Limb Based Patency
HES	-	Hospital Episode Statistics
BS	-	Bypass Surgery

MI	-	Myocardial Infarction
CVA	-	Cerebro-Vascular Accident
PTA	-	Percutaneous Transluminal Angioplasty
ITS	-	Immediate Technical Success
TASC	-	Trans-Atlantic Inter-Society Consensus Document

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

1 Meecham L, Bate G, Patel S, Bradbury AW. A comparison of clinical outcomes following femoropopliteal bypass or plain balloon angioplasty with selective bare metal stenting in the Bypass versus Angioplasty in Severe Ischaemia of the Limb (BASIL) Trial. Eur J Vasc Endovasc Surg. 2019 Jul;58(1):52-59

2 Meecham L, Patel S, Bate G, Bradbury AW. Editors Choice – A comparison of clinical outcomes between primary bypass and secondary bypass after failed plain balloon angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial. Eur J Vasc Endovasc Surg. 2018 May;55(5):666-671

3 Meecham L, Popplewell M, Bate G, Patel S, Bradbury AW. Comparison of femoropopliteal plain balloon angioplasty for chronic limb-threatening ischaemia in the BASIL trial and in a UK contemporary series. J Vasc Surg. 2021 Dec;74(6):1948-1955

4 Meecham L, Popplewell M, Bate G, Patel S, Bradbury AW. Contemporary (2009-2014) clinical outcomes after femoro-popliteal bypass surgery for chronic limb threatening ischaemia are inferior to those reported in the UK Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial (1999-2004). J Vasc Surg. 2019 Jun;69(6):1840-1847.

5 L Meecham, Popplewell MA, Bate G, Patel S, Bradbury AW. A comparison of contemporary clinical outcomes following femoro-

popliteal plain balloon angioplasty and bypass surgery for chronic limb threatening ischaemia. Vasc Endovasc Surg. 2021 Aug;55(6):544-550.

6 Meecham L, Popplewell M, Bate G, Davies HOB, Kodama A, Conte MS, BradburyAW. Evaluation of the Global Anatomic Staging System in patients with chronic limb threatening ischaemia undergoing endovascular intervention for femoro-popliteal disease. J Vasc Surg. 2022 Sep 12;S0741-5214(22)02242-X (Online)

LIST OF PRESENTATIONS ARISING FROM THIS THESIS

1 A comparison of clinical outcomes following femoropopliteal bypass or plain balloon angioplasty with selective bare metal stenting in the Bypass versus Angioplasty in Severe Ischaemia of the Limb (BASIL) Trial. Oral Presentation European Society of Vascular Surgery, Valencia 2018.

2 Clinical outcomes after femoro-popliteal bypass surgery are worse now (2009-2014) than they were in the original Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial (1999-2004). Controversies & Updates in Vascular Surgery, Paris 2018.

3 A comparison of clinical outcomes between primary bypass and secondary bypass after failed plain balloon angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial. Oral Presentation Vascular Society of Great Britain and Ireland, Manchester 2017.

4 Comparison of femoropopliteal plain balloon angioplasty for chronic limb-threatening ischaemia in the BASIL trial and in a UK contemporary series. Oral Presentation, Vascular Society of Great Britain and Ireland, Manchester 2017

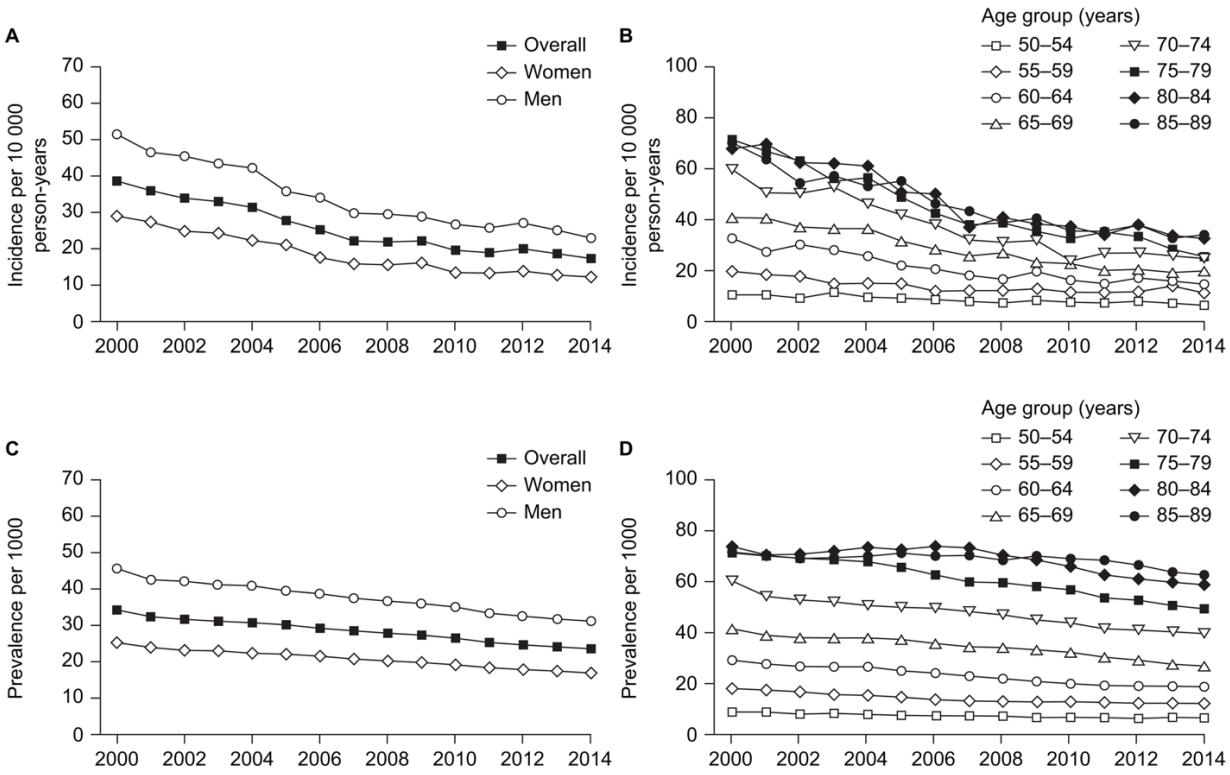
1 INTRODUCTION

1.1 SETTINGS AND AIMS

Patients suffering with peripheral arterial disease (PAD) are separated into three groups: asymptomatic peripheral arterial disease (APAD), intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI). Proportions suffering with each vary in differing populations, most recent data from a randomized cohort in Sweden report APAD in 11%, IC in 6% and CLTI in 1% of the studied population(1) and are consistent with that reported in the TASC-II guideline ten years earlier (2007) (2).

The most recent population-based evidence generated in the United Kingdom (UK) confirms the incidence of PAD is declining. The incidence of PAD has decreased by half at a rate of 38.55 per 10,000 person years in the year 2000 to 17.33 per 10,000 person years in 2014. This trend is consistent across the sexes, with a higher incidence in men (23.05 vs 12.37 per 10,000 person years respectively in 2014). The overall decrease in incidence was paralleled by a decrease in prevalence over the same time period (3.42% to 2.37%)(3).

Figure 1.1.1 *Histogram of incidence and prevalence of PAD in UK population over time.*



These figures are comparable to other studies that have been published in Europe and the United States of America (USA) (4, 5), however are contradictory with a large meta-analysis published in the Lancet in 2013 which claimed increasing global prevalence of PAD (6), it would seem that in low and middle income countries the reverse trend is observed (perhaps due to ageing population, high rates of smoking and diabetes and poor access to health care).

All efforts should be made to prevent progression of disease in patients with a diagnosis of PAD. Often patients do not decline in a linear pattern, and may progress straight from APAD to CLTI, due to trauma or thrombosis in situ. It is estimated that 8.5% of patients suffering with APAD or IC will progress to CLTI. Overall European or

North American countries will experience 500-1000 new cases of CLTI per Million population annually (2).

Patients with PAD are known to have increased all-cause mortality compared to those that do not. In the Swedish study cited earlier 10-year follow up revealed mortality in non-PAD, APAD, IC and CLTI patients was 27%, 56%, 63% and 75% respectively (1).

Table 1.1.1 *Comparison of mortality rates of common cancers versus CLTI*

Disease	5-Year Mortality Rate
CLTI-without amputation	55-65%
Female Breast Cancer	10%
Bladder Cancer	23%
Colon Cancer	35%
Myeloma	50%
Lung and Bronchus Cancer	82%
Pancreatic Cancer	92%

Barnes et al. Epidemiology and Risk of Amputation in Patients With Diabetes Mellitus and Peripheral Artery Disease (7)

1.2 PREVIOUS DEFINITIONS AND CLASSIFICATION OF CLTI

1.2.1 Classification

Classification of PAD is essential to stratify patients and determine the need for treatment. The two systems most commonly used in clinical practice are the Fontaine (8) and Rutherford (9).

Table 1.2.1.1 *Fontaine classification of peripheral arterial disease*

Fontaine classification	Clinical status of the limb
1	Asymptomatic
2	Claudication
3	Ischaemic rest pain
4	Ulceration or Gangrene

Broadly, Fontaine's classification is adequate and defines the four main groups of patients with PAD, we have since come to understand that differing clinical pictures are present within these four categories. The system was further developed by Rutherford, who separated claudication and tissue loss into further categories and provided objective haemodynamic measurements to classify patients.

Table 1.2.1.2 *Rutherford classification of peripheral arterial disease*

Category	Clinical Description	Objective Criteria
0	Asymptomatic	Normal treadmill test
1	Mild Claudication	Completes treadmill exercise, Ankle pressure (AP) post exercise >50mmHg but at least 20mmHg lower than resting value
2	Moderate Claudication	Between categories 1 and 3
3	Severe Claudication	Cannot complete exercise test and AP post exercise <50mmHg
4	Ischaemic Rest Pain	Resting AP <40mmHg, TP< 30mmHg
5	Minor Tissue Loss	Resting AP <60mmHg, TP <40mmHg
6	Ulceration or Gangrene	Same as category 5

Rutherford added objective measurements (arterial pressure) to the classification in attempt to improve accuracy of patient stratification. This also highlighted to clinicians that poor circulatory pressure was associated with poorer healing and worse outcomes.

1.2.2 Defining Chronic Limb Threatening Ischaemia

CLTI is numerically defined as an ABPI <0.4 or an absolute ankle pressure of <50 mmHg or an absolute toe pressure <30mmHg (10). In patients with Diabetes Mellitus (DM) or end stage renal failure (ESRF), where medial calcinosis is more likely TBPI should be performed (11). The Global Vascular Guideline (GVG) caution against using specific ABPI or TBPI thresholds to diagnose CLTI. Instead, they recommend using these pressures in conjunction with doppler analysis (looking for damped waveforms) to decisively conclude the state of perfusion of the threatened limb.

1.2.3 Important endpoints in CLTI

Amputation Free Survival (AFS)

Individual is still alive without major lower limb amputation of the index limb at the end of the study period.

Overall Survival (OS)

Individual reaches the end of the study period and is alive.

Limb Salvage (LS)

Individual is alive or dead without major lower limb amputation of the index limb.

Freedom from re-intervention (FFR)

Individual reached end of study period without a return to theatre for post-operative complications or further attempted re-vascularisation of the affected limb.

Major Adverse Limb Event (MALE)

Return to theatre for post-operative complication (e.g. bleeding/occlusion), further attempted re-vascularisation or major lower limb amputation of the index limb.

Major Adverse Limb Event free Survival (MALE-S)

Surviving to the end of the study period without; return to theatre for post-operative complication, further attempted re-vascularisation or major lower limb amputation of the index limb.

Major Adverse Cardiovascular Event (MACE)

Post intervention myocardial event, coronary revascularisation or cerebrovascular event (transient ischaemic attack or cerebrovascular accident).

Minor Amputation

Any amputation performed below the ankle.

Major Lower Limb Amputation (MLLA)

Any lower limb amputation above the ankle (Below Knee Amputation, Through Knee Amputation or Above Knee Amputation).

1.3 EVIDENCE AND GUIDELINES IN CHRONIC LIMB THREATENING ISCHAEMIA

Even though the vascular community recognise CLTI as an important problem with significant clinical consequences for patients, the evidence base is poor. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial is the only randomised controlled trial (RCT) investigating whether an open surgical revascularisation or endovascular revascularisation first strategy provides best clinical outcomes. In terms of which bypass conduit to use, the most comprehensive study was produced 30 years ago by Veith (12) who demonstrated quite convincingly that vein bypass, particularly to the below knee popliteal (BK-pop) and tibial vessels was far superior in terms of patency. A more recent study corroborated these findings (13). In terms of endovascular revascularisation or synthetic conduit for open surgical bypass (OSB) nearly all of the trials are industry sponsored and designed to achieve regulatory approval on safety grounds rather than on grounds of clinical superiority (non-inferiority design, small patient numbers). The bulk of the literature consists of trials comparing technical outcomes in terms of technical success and patency and neglect the most important clinical outcomes (OS, LS, AFS, MALE). They also mix patient cohorts with the vast majority suffering with IC rather than CLTI. The case for adopting newer endovascular devices (drug coated balloons (DCB), drug eluting stent (DES), covered stent, lithotripsy, directional atherectomy) is made in comparison to plain balloon angioplasty or bare metal stent mainly in patients with IC. None are compared to the 'Gold standard' vein bypass. In recent times, there has been an effort to fill this knowledge gap with large publicly funded RCT's (BASIL 2 (14) and 3 (15), BEST-CLI (16) and SWEDEPAD 1 and 2 (17) and are discussed below.

1.3.1 Bypass versus Angioplasty in severe ischaemia of the leg trial (BASIL)

The UK National Institute of Health Research Health Technology Programme (NIHR HTA) funded Bypass versus Angioplasty for Severe Ischaemia of the Leg trial, now known as the BASIL-1 trial, remains the only published RCT to have compared an OSB first with a plain balloon angioplasty, with or without bare metal stenting, (PBA +/- BMS) first revascularisation strategy for chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease (18-20). In brief, between August 1999 and June 2004, 452 patients with CLTI due to infra-inguinal disease were randomised to an OSB first or a PBA +/- BMS first revascularisation strategy. Patients were eligible for trial inclusion if the responsible clinicians felt that they required early revascularisation and were in clinical equipoise between OSB and PBA +/- BMS. Patients were followed up by six dedicated research nurses at 1, 3, 6, and 12 months post randomisation and then annually until death or 1 July 2007. The primary endpoint was amputation free survival (AFS) and secondary end-points included overall survival (OS), limb salvage (LS) and requirement for re-intervention. BASIL-1 was a multi-centre, pragmatic, clinical effectiveness RCT that allowed participating units to continue to use their preferred post-intervention surveillance programmes. However, the majority of the re-interventions were due to persisting or recurrent symptoms and signs of CLTI.

Approximately 75% of patients had predominantly femoro-popliteal (FP) disease and intervention while in about 25% the disease and intervention were predominantly infra-popliteal (IP). A recently published BASIL-1 IP sub-group analysis showed that, when compared to PBA (no IP BMS were used), a vein bypass (VB) first strategy resulted in better (OS), (AFS), and quality of revascularisation (time to wound healing and relief

of ischaemic rest pain)(21). Despite BASIL-1, the only currently available 'level 1' evidence, showing better long-term clinical outcomes following OSB, there has nevertheless been a non-evidence-based trend towards offering primary endovascular intervention to patients with CLTI due to FP disease.

1.3.2 Global Vascular Guidelines on Chronic Limb Threatening Ischaemia

The GVG are the most recent and comprehensive guidelines written specifically for the management of patients suffering CLTI. These guidelines will be the cornerstone for worldwide management of CLTI and therefore will be the guidelines used for comparison within this thesis. They are discussed in detail in their own section.

1.3.3 National Institute for Clinical Excellence Clinical Guideline 147 (NICE CG 147)

NICE guidelines form the basis of all treatment decisions in the UK national health service (NHS). First published August 2012 (22) and last updated February 2018, CG 147 concerns the diagnosis and management of PAD and therefore includes guidelines on patients with IC and CLTI, these patients are considered separately within the guideline. Recommendations are made regarding best medical therapy (BMT) (Smoking cessation, control of hypertension and diabetes mellitus, antiplatelet and statin therapy).

Below are the recommendations for patients with CLTI:

Secondary prevention of cardiovascular disease

- All patients should be offered the following:
    - Smoking cessation
    - Diet, weight management and exercise
    - Lipid modification and statin therapy
    - Prevention, diagnosis and management of DM
    - Prevention, diagnosis and management of Hypertension
    - Antiplatelet therapy

Diagnosis

- Thorough history and examination
- Measuring ABPI (patients without DM)

Imaging for Revascularisation

- Offer duplex ultrasound as first-line imaging to all people with PAD for whom revascularisation is being considered
- Offer contrast enhanced magnetic resonance angiography to people with PAD who need further imaging.
- Offer computed tomography angiography to people with PAD who need further imaging if contrast-enhanced magnetic resonance angiography is contraindicated

Revascularisation of Infra-Inguinal Disease

- Offer angioplasty or bypass surgery for treating people with critical limb ischaemia who require revascularisation
- **Do not** offer primary stent placement for treating people with critical limb ischaemia caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease
- Use bare metal stents when stenting is used for treating people with critical limb ischaemia
- Use an autologous vein whenever possible for people with critical limb ischaemia having infra-inguinal bypass surgery

Management of ischaemic rest pain

- Offer paracetamol, and either weak or strong opioids depending on the severity of pain, to people with critical limb ischaemic pain
- **Do not** offer chemical sympathectomy to people with critical limb ischaemic pain, except in the context of a clinical trial

Major Amputation

- **Do not** offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team

NICE Clinical Guideline 147

Very few changes were made to the original document in the 2018 revision, reflecting the deficiency of new evidence in CLTI during that time period. NICE emphasises the importance of baseline risk factors modification for patients with PAD. The majority of patients with PAD will suffer cardiovascular death, hence the importance of antiplatelet and statin therapy along with control of blood pressure (BP) and diabetes mellitus (DM). Although considered as standard care, implementation of BMT can still be improved. These guidelines were the reference when patients included in this thesis were treated, the GVG are now used in conjunction with NICE CG147 to inform clinical decision making in every aspect of care for patients with CLTI.

1.3.4 The Bypass versus Angioplasty in severe ischaemia of the leg - 2 (BASIL- 2) trial

The Bypass versus Angioplasty in Severe Ischaemia of the Leg - 2 (BASIL-2) Trial is a UK NIHR-HTA funded, multi-centre randomised controlled trial (http://www.nets.nihr.ac.uk/projects/hta/123545) that will compare, at the point of clinical equipoise, the clinical and cost-effectiveness of a 'vein bypass first' with a 'best endovascular treatment first' revascularisation strategy for severe limb ischaemia due to IP (below the knee) disease (14). The trial was funded based on the dearth of evidence supporting IP intervention for CLTI. As the vast majority of patients (>75%) underwent femoro-popliteal (FP) intervention in BASIL-1, the results mainly reflect outcomes of treating FP disease. NICE CG 147 identified this area as a research priority in PAD and hence the concept and design of BASIL-2. BASIL -2 has been on-going since 2014 and has had major challenges to recruitment, it has now closed to recruitment on 345 patients, 45 short of the calculated target of 380 patients. Initially,

based on the observed event rates in BASIL-1, it was calculated that 600 patients (300 in each arm) were required to detect a one third reduction (hazard ration 0.66) in AFS at a mean follow up 3 years with 90% power. These figures were based on observing 247 events in the trial cohort; slower than expected recruitment has resulted in longer than anticipated follow up coupled with a higher than expected event rate, resulting in a revised sample size of 380 patients to achieve the same statistical power.

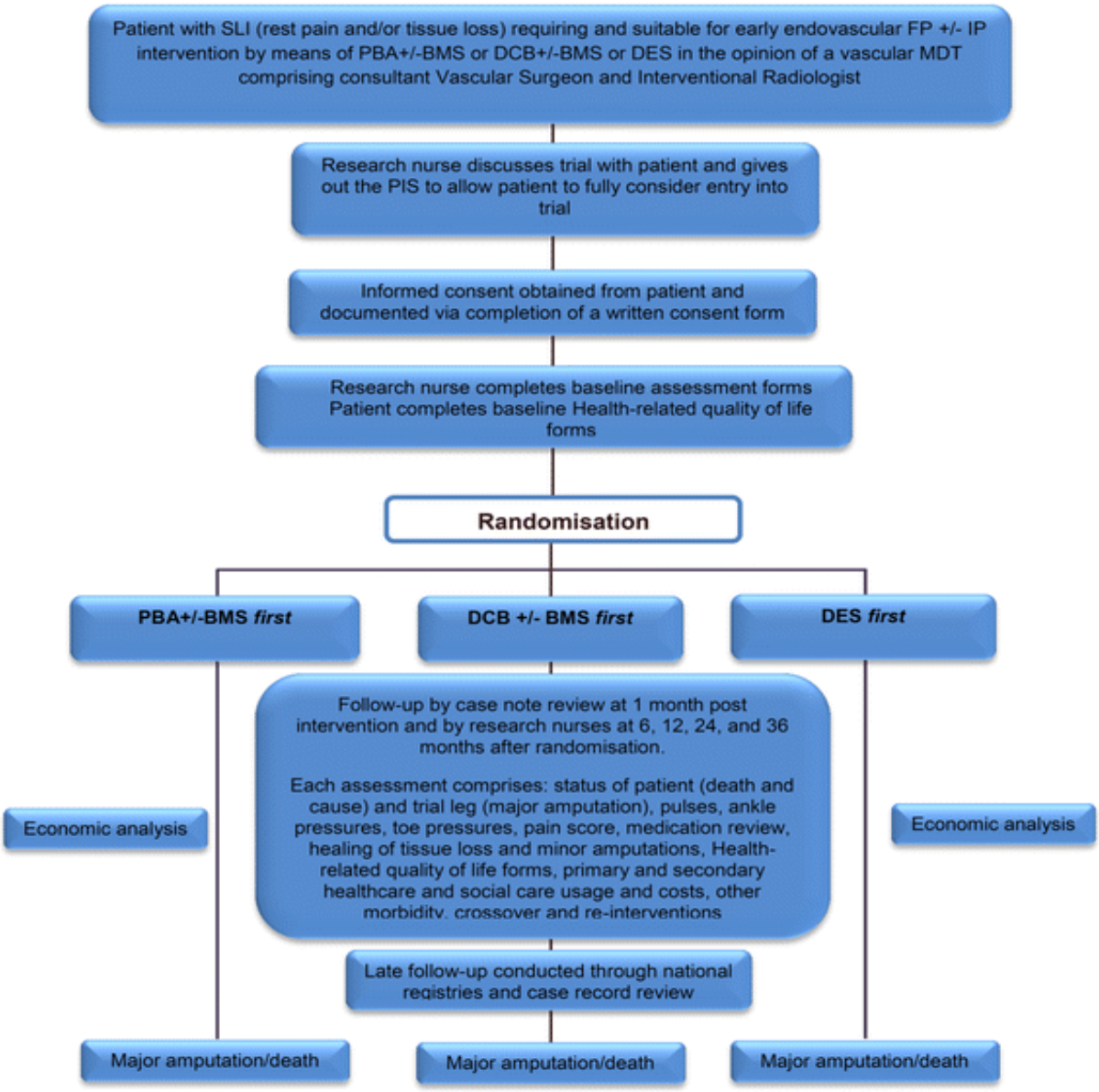
1.3.5 The BAlloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3) trial

Along with very little evidence for interventions in the IP segment, drug eluting technology in the form of Paclitaxel coated angioplasty balloons and impregnated stents have started to become part of routine care despite very little objective evidence demonstrating clinical and cost efficiency. This was recognised by the NICE guideline development committee and was also prioritised as an area of urgent need of research, to that end the NIHR-HTA funded a sister trial to BASIL 2, the BAlloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3) trial (15). This FP trial compares standard treatment (plain balloon angioplasty with bailout bare metal stent (PBA+/-BMS)) with drug coated ballon +/- BMS or primary drug eluting stent. To ensure that the results between all three trials are suitable for comparison the primary outcome is AFS and all other important clinical outcomes are being collected and analysed (LS, OS, MALE, MACE).

Again the sample size calculation was based on event rates in the endovascular arm of BASIL-1. The study was powered at 90% to detect a hazard ratio of 0.60 for both comparisons reducing the risk of the primary outcome (AFS). Across the three arms,

a total of 342 events would be required to detect a hazard ratio of 0.60 at the 2.5% significance level. Conservatively, allowing for 5% drop out for the primary outcome (equivalent to 1% dropout in each year for 5 years) a total of 861 participants were required. As with BASIL-2, slow recruitment (and a halt period due to the Katsanos (23) meta-analysis) leading to longer follow up and a higher than anticipated event rate has led to a decrease in the sample size required (now approx. 477), the trial has completed recruitment and is currently in the follow up phase, it is anticipated that the results of BASIL-3 will be reported in the first quarter of 2024.

Figure 1.3.5.1 *Consort diagram for the BASIL -3 trial*



1.3.6 SWEDEPAD 1&2

The Swedish Drug-Elution trial in Peripheral Arterial Disease (SWEDEPAD) 1 and 2 registry based RCT opened to recruitment in 2014 and aims to determine the clinical and cost effectiveness of Paclitaxel drug devices in patients with CLTI (SWEDEPAD 1) and intermittent claudication (SWEDEPAD 2). They aim to recruit a total of 3800 patients and will report on a primary outcome of AFS and health related quality of life (HRQL).

SWEDEPAD have released their first interim analysis attempting to address the safety concerns raised by Katsanos et al. and whether it is safe and ethical to continue recruitment into the trial. At the time of analysis 2289 patients were enrolled (1408 with CLTI and 809 with IC) with no significant difference in mortality between the two groups (mean follow up 2.49 years, 25.5% mortality drug coated group and 24.6% mortality uncoated group, HR 1.06). This trend was consistent when analysed at 1 year follow up (10.2% vs 9.9%) and by classification of PAD (33.4% and 33.1% in CLTI, and 10.9% and 9.4% in IC). They have concluded that there is no short and medium-term excess risk to drug coated devices and have resumed randomisation(17).

1.3.7 Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) Trial

In the United States of America (USA) the National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI) Best Endovascular versus Best Surgical Therapy in patients with Critical Limb Ischaemia (BEST-CLI) is the largest publicly

funded RCT into CLTI. BEST-CLI includes all patients with infra-inguinal disease requiring revascularisation and groups the patients into two separate cohorts, those with (cohort 1) and without (cohort 2) single segment autologous great saphenous vein (GSV) that can be used as a conduit. Those with GSV were randomised to receive OSB or best endovascular therapy (BET) (intended sample size – 1620). Those without GSV were randomised to receive an alternative conduit OSB (Arm vein/Synthetic) or BET (intended sample size – 480) (16).

Like BASIL-2 and 3, BEST CLI struggled with recruitment, leading to closure to recruitment at 1,843 randomised patients (from a target of 2100). Due to financial constraints follow up was limited to 24 months post final recruit in cohort 1 (mean 2.7 years) and stopped early (mean 1.7 years) in cohort 2. Despite under recruiting and shorter than intended follow up the trial met a statistically significant endpoint; surgery first strategy (in patients with GSV) had a 32% lower risk of Major Adverse Limb Event or Death. This was mainly driven by major re-intervention and MLLA, however there was a non-significant trend to better survival in the OSB group (Cohort 1). Cohort 2 did not demonstrate any significant difference in the observed clinical endpoints, indicating a patient targeted intervention in patients with no GSV is appropriate (24).

The BEST-CLI and BASIL trialists have agreed to perform an individual patient data meta-analysis once both trials have reported to further increase the available level 1 evidence in infra-inguinal CLTI.

1.4 GLOBAL VASCULAR GUIDELINES ON CHRONIC LIMB THREATENING ISCHAEMIA

The global vascular guidelines (GVG) have been produced by non-industry funded experts in vascular disease from over 30 countries representing the Society for Vascular Surgery of North America (SVS), The European Society of Vascular Surgery (ESVS) and the World Federations of Vascular Societies (WFVS). Their brief is to produce guidelines based on best evidence for the treatment of CLTI that can be adopted worldwide. The first guideline has been published synchronously in the Journal of Vascular Surgery (JVS) (25) and the European Journal of Vascular and Endovascular Surgery (EJVES)(26). This is a comprehensive document, which provides recommendations based on the current evidence and introduces new ways of working to standardise the approach to CLTI world-wide. With regard to diagnosis, investigation and medical management the recommendations are in line with the other published national and international guidelines. They recommend stratifying patients by preintervention anatomical and disease severity scoring to aid evidence-based revascularisation. Firstly, they have introduced the Global Limb Anatomic Staging System (GLASS score) to stratify the likelihood of successful and sustained endovascular revascularisation based on the anatomy of the diseased vessels and the target artery path (TAP). Secondly, they advocate the routine use of the Society of Vascular Surgery (SVS) (27) threatened limb tool - WIfI (**W**ound, **I**schaemia and **f**oot **I**nfection) to stratify severity of disease in the foot, with the understanding that patients with more severe disease are likely to require bypass surgery in favour of endovascular revascularisation. These tools should be used to facilitate evidence-based revascularisation: PLAN (Patient risk estimation, Limb staging (WIfI), Anatomic

pattern of disease (GLASS), No option anatomy). PBA is regarded as the standard method of endovascular revascularisation with other devices to be used as adjuncts in cases of poor technical result or poor flow. Autologous vein should be the conduit of choice for surgical bypass; when absent, synthetic bypass should be used after failed attempted endovascular revascularisation. Intra-operative imaging should be performed to identify any technical deficits that can be resolved prior to finishing the case.

The GVG recommends enrolling patients who have undergone vein bypass in a clinical surveillance programme with or without ultrasound for 2 years. Significant stenosis (>70%) should be treated to maintain graft patency and surveillance period should be reset after each graft-based intervention.

The GVG make research recommendations regarding understudied topics in the literature, and reporting standards of prospective trials to standardise outcomes for good amalgamation of data for meta-analysis. Specifically, they recommend that all regulatory trials aimed at obtaining pre-market approval for use in CLTI should use CLTI patients and report clinical as well as anatomical outcomes. Finally, they recommend new devices should be monitored in well designed, large observational studies and registries to inform long term outcomes in real world practise.

In short, the GVG aim to improve current and future outcomes for patients suffering with CLTI by:

1. Defining CLTI and proposing a structured approach to diagnosis and investigation
2. Promoting paradigms and tools that support EBR
3. Making specific practice recommendations based on GRADE* levels of evidence

4. Identifying gaps in the evidence and suggesting areas and methods for future research.

*GRADE – Grading of Recommendations, Assessment, Development and Evaluations

1.4.1 Initial Patient assessment

As with any other medical or surgical condition, patients presenting with suspected CLTI should undergo a thorough history and clinical examination (including systemic observations such as blood pressure (BP), pulse, oxygen saturations, weight (KG) and Height (cm)).

1.4.2 Non-invasive haemodynamic testing

ABPI is calculated using the pressure at the brachial artery as well as those recorded at the Dorsalis Pedis (DP) and Posterior Tibial (PT) Arteries using the following formula:

$$\text{ABPI} = \frac{\text{Ankle Systolic Pressure (mmHg)}}{\text{Brachial Systolic Pressure (mmHg)}}$$

ABPI should be interpreted with caution in patients suffering with DM and ESRF, calcification of the arteries can lead to artificially high if not incompressible values. In these patients toe pressures provide a more accurate haemodynamic assessment.

A TBPI ratio of >0.7 is considered normal as opposed to >0.9 for ABPI (10). It is currently quoted that a patient with CLTI and an absolute toe pressure of <30mmHg will not heal their wound without revascularisation(28).

Table 1.4.2.1 *Ankle Brachial Pressure Index and correlation with disease severity*

Resting ABPI	Severity of disease
>1.4	Calcified vessels
>1.0	No arterial disease
0.81-1.00	No arterial disease/mild, insignificant disease
0.5-0.8	Moderate disease
<0.5	Severe disease
<0.3	Critical ischaemia

The GVG recommend performing an ankle pressure (AP) and ABPI on all patients being assessed for CLTI.

1.4.3 The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI).

The Society of Vascular Surgery (SVS) Wound Infection and Foot ischaemia (WIfI) tool has been developed to more accurately stratify patients into groups concerning their risk of limb loss (27). It recognises that in patients with CLTI, ischaemia is not the only determining factor for limb loss. Infection and degree of tissue loss are equally important and only by including these aspects in the assessment of patients can we accurately stratify their risk. WIfI has been validated within the USA population (29, 30); increasing WIfI stage is associated with a significantly increased risk of limb loss.

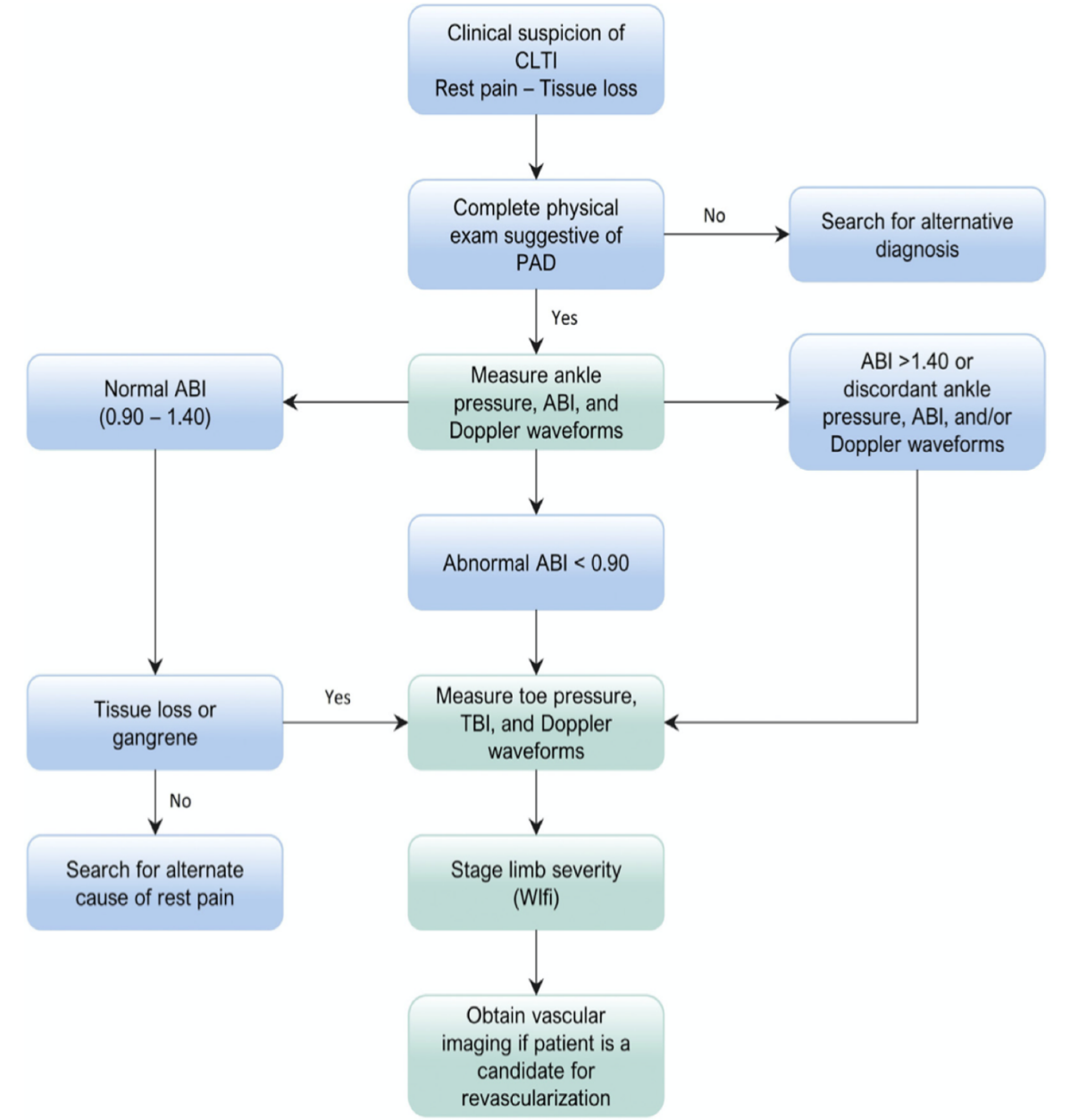
The GVG propose that all patients with CLTI undergo WIfI scoring prior to any intervention.

1.4.4 Perfusion, Extent, Depth, Infection and Sensation (PEDIS)

This scoring system was developed specifically to assess foot wounds in the diabetic population(31). Each of the five domains are assessed and scored according to pre-defined criteria. The PEDIS system has been validated in the diabetic foot cohort; it is being used to assess patients in the BASIL-2 and 3 trials. The GVG are recommending the use of the WIfI system for stratification of CLTI patients because it more accurately stratifies for degree of ischaemia, and permits use in non-diabetics.

1.4.5 Global Vascular Guidelines investigation pathway for CLTI

Figure 1.4.5.1 *Global Vascular Guideline Proposed investigation pathway for patients with suspected CLTI*



1.4.6 Non-Invasive Imaging

1.4.6.1 Duplex Ultrasound (DUS)

Duplex Ultrasound (DUS) is a non-invasive method of imaging the vascular tree. This method is able to visualise the arteries using ultrasound (US) technology and is also able to detect flow using the Doppler concept. DUS has reasonably high sensitivity (88%) and specificity (>95%) however is user dependent (32). It is a test that can be applied at the bedside and can be utilised in almost all clinical scenarios. It does however have its limitations, the largest being its operator dependence. Also, in very calcified vessels views are limited, calcification prevents propagation of ultrasound (US) waves and therefore casts acoustic shadows, in patients with significant vessel calcification DUS may be quite unreliable.

1.4.6.2 Computed Tomography Angiography (CTA)

Nearly all computed tomography (CT) scanners in the UK have the ability to perform angiography. CTA provides accurate anatomical pictures of the arterial tree and also allows the physician to assess the other associated anatomy. It has > 90% sensitivity and specificity and is the recommended imaging modality for aorto-iliac disease (32). It can allow for quantification of arterial disease but can often be inaccurate in the vessels below the knee due to their small diameter (1-3mm) especially if there is arterial calcification (33, 34). The benefits of CT imaging have revolutionised the treatment of arterial disease and procedural planning, there are however many limitations. CTA requires ionizing radiation, repeated exposures to patients does increase their lifetime risk of malignancy (35, 36). As well as radiation, contrast

medium is nephrotoxic, which is often problematic in patients suffering with peripheral vascular disease as many have associated chronic kidney disease (CKD) (37).

1.4.6.3 Magnetic Resonance Angiography (MRA)

MRA is a less frequently utilized technique of arterial imaging as it requires significantly more time to acquire the number of images compared to CTA. MRA doesn't provide good quality images of surrounding structures like CTA however does give a more accurate representation of the arterial lumen with >90% sensitivity and specificity (38). MRA's clear advantage over CTA is in crural vessel (Anterior Tibial (AT), Posterior Tibial (PT) and Peroneal artery PP)) imaging (39). Although not as accurate as Digital Subtraction Angiography (DSA) MRA has been shown to provide excellent imaging of this smaller aspect of the arterial tree (40). The main limitation to MRA is the time required to acquire images, it usually involves a patient laying still for 45 minutes, and poorly tolerated by patients who suffer with claustrophobia. It is contra-indicated in patients who have recently undergone surgery, those who have a pacemaker in situ or those with metallic implants that may be susceptible to magnetism. Rarely those with very poor renal function may develop nephrogenic systemic fibrosis, however the incidence of this complication is exceedingly rare (41).

1.4.7 Invasive Imaging

1.4.7.1 Digital Subtraction Angiography (DSA)

DSA is still the gold standard investigation for PAD, however, is used as second line due to its invasive nature (42). Patients undergo direct cannulation of the arterial tree under local anaesthesia and have real time dynamic images produced with intra-arterial contrast. The soft tissues and bones are 'subtracted' from the image prior to the injection of arterial contrast to provide only a view of the arterial lumen, and as it's a dynamic test, an idea of flow quality can be estimated. DSA is still the investigation of choice to plan distal bypass surgery as no other imaging modality is able to provide the required level of detail to accurately assess the quality of outflow for any potential bypass. DSA does have limitations, direct arterial puncture can often be painful for the patient and is associated with local complications such as bleeding and occlusion of the artery. Nephrotoxic contrast is used and therefore can be contra-indicated in people with significant kidney disease (37). DSA is often reserved for patients who are likely to go on to invasive intervention.

1.4.8 Patient risk estimation, Limb, Anatomy (PLAN)

1.4.8.1 Patient Risk Estimation

All patients with suspected CLTI should be referred to a vascular service for evaluation and consideration of revascularisation (GVG-Good Practise Statement). Numerous risk stratification tools have been developed (only on patients undergoing revascularisation) in an effort to stratify patient risk (BASIL (43), Finnvasc (44),

PREVENT III (45) etc), unfortunately, none have been fully validated and so not one can be recommended over others. As well as specific tools, there is growing interest and evidence that assessing frailty helps identify those patients who would be high risk for revascularisation(46). For now, until a more reliable and comprehensive risk assessment tool can be validated, each unit should standardise their method for assessing patients' fitness for revascularisation and select strict criteria for who is and isn't suitable for intervention.

1.4.8.2 Limb Staging

Patients suffering with CLTI present with a broad spectrum of disease, staging is essential in understanding the risk of limb loss. The GVG recommend the use of the SVS Threatened Limb Classification as the tool of choice in CLTI patients. All symptomatic patients with WIfI grade 3 / 4 (Severe limb threat) should undergo revascularisation. If the patient is suffering with WIfI grade 4 disease (due to advanced tissue loss/gangrene) revascularisation is likely to be beneficial even if the degree of ischaemia is relatively modest. Patients with WIfI grade 1-2, who have a lesser degree of tissue loss or infection but mild to moderate ischaemia are often treated successfully with conservative measures (Infection control, analgesia, dressings and podiatric interventions), although must be watched carefully and re-staged regularly, with intervention if wounds deteriorate or fail to progress.

1.4.8.3 Anatomy of Disease

The GLASS score is yet to be fully validated and will require adjustment to improve its predictive accuracy. The evidence for optimal revascularisation strategy is poor, with BASIL-1 being the only multicentre RCT addressing this question. It is hypothesised that the durability of endovascular revascularisation decreases as the GLASS stage increases, and some studies have confirmed this (in terms of Immediate Technical Success (ITS) and MALE)(47). As there is growing evidence that the outcomes of secondary bypass after failed endovascular intervention are inferior to those of primary bypass it is essential to choose the appropriate revascularisation strategy to maximise the chance of successful outcome. The GVG recommend performing vein bypass surgery for patients with GLASS stage 3 disease. There is also some evidence that outcomes in patients with advanced tissue loss or gross infection, endovascular intervention are inferior to vein bypass, which seems to be the optimal intervention.

1.4.9 Global Anatomic Limb Staging System (GLASS)

The GLASS score is a newly developed scoring system, that attempts to quantify the likelihood of success of endovascular revascularisation in patients with infra-inguinal occlusive disease. The GLASS score requires a designated TAP be allocated for scoring. This is in line with the current thinking that restoration of in-line flow to the foot provides the best chances of wound healing in patients with CLTI. The GLASS score considers the femoro-popliteal and infra-popliteal segments of the TAP separately and scores the severity of disease from grade 0-4 (4 being the worst). It is the first scoring system to include the degree of calcification as a negative factor in

outcome, with calcified vessels being upgraded one grade. The pedal circulation is also scored (0-2) to provide an understanding of circulation in the foot arch, and considered when choosing the TAP and approximate likelihood of establishing in line flow. Both IP and FP disease scores are then combined to provide a GLASS stage between 1-3. The GLASS stage defines the likely success of attempted endovascular revascularisation along the TAP. The GLASS score is newly developed and as yet has not been validated. Part of this thesis will be to validate the GLASS score in patients with FP disease undergoing endovascular intervention.

Figure 1.4.9.1 *Methodology for grading the Femoro-popliteal and Infrapopliteal segment in the GLASS score*

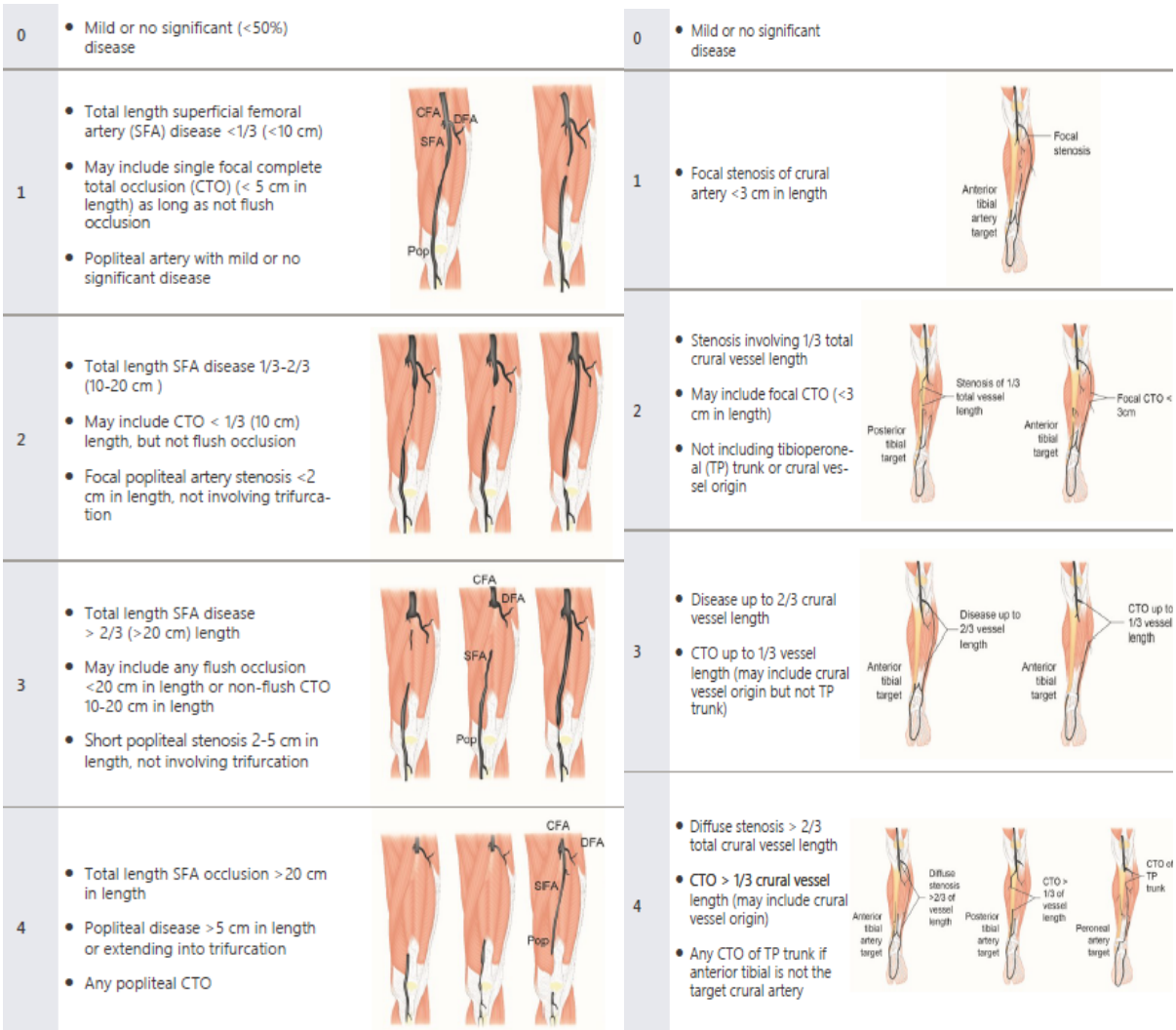


Figure1.4.9.2 *Matrix for allocating patients into GLASS stage*

		INFRAINGUINAL GLASS STAGE				
FP Grade	4	III	III	III	III	III
	3	II	II	II	III	III
	2	I	II	II	II	III
	1	I	I	II	II	III
	0	NA	I	I	II	III
		0	1	2	3	4
		IP Grade				

*severe calcification (e.g. >50% of circumference, diffuse, bulky, or "coral reef" plaques) within the TAP increases the within-segment **grade** by **+1**

1.5 MANAGEMENT OF FEMORO-POPLITEAL INDUCED CHRONIS LIMB THREATENING ISCHAEMIA

1.5.1 Best Medical Therapy

Medical optimisation of patients suffering with PAD is imperative. These patients are subject to an excessively high risk of cardio-vascular complications including Myocardial Infarction and ischaemic or haemorrhagic stroke. The goal in medical management is to:

1. Reduce the risk of concurrent cardio-vascular disease (CVD) morbidity/mortality
2. Control risk factors such as hypertension, hypercholestrolaemia, DM and smoking to prevent further progression of atherosclerotic disease
3. Maintenance of revascularisation e.g. bypass graft patency.

1.5.1.1 Antiplatelet agents

All major national and international society and government organisation guidelines recommend the use of antiplatelet agents in patients diagnosed with PAD. The bulk of the evidence for the recommendations are based on trials investigating primary and secondary prevention of major adverse cardiac events (MACE). Seminal trials investigating the benefits of antiplatelet agents in patients with CVD underwent meta-analysis by the Antithrombotic Trialists' Collaboration, they analysed 135,000 patients with CVD versus 77,000 controls and found a 22% reduction in MACEs in patients receiving antiplatelet therapy. They also concluded that 75-150mg once daily (OD) Aspirin was as effective as higher doses with significantly decreased bleeding risk

(48). The same effect was observed in a more recent meta-analysis performed by the same collaboration, confirming the benefits of aspirin in secondary prevention (49). A similar effect has been observed in those patients with CLTI, there was a 64% reduction in vascular events in those patients taking 100mg Aspirin in the CLIPS study (50). Aspirin has been the traditional antiplatelet of choice, owing to the large body of evidence which supports its benefits, the medical community has been looking to other antiplatelet agents to further decrease events. The CAPRIE trial, was designed to assess the antithrombotic and safety effects of 75mg of clopidogrel OD versus 310mg of aspirin in patients who had PAD. Those receiving clopidogrel had an 8% reduction in MACEs with no significant difference in bleeding risk (51). The protective effect is also observed in other antiplatelet agents (52, 53) however these have not been shown to outperform clopidogrel. The most recent large-scale trial, EUCLID, compared ticagrelor with clopidogrel in >13,000 patients. Ticagrelor demonstrated equivalent safety profile but did not outperform clopidogrel (54).

Combination of aniplatelet therapy is an area of ongoing investigation, currently there is no evidence to support its routine use in the primary or secondary prevention of MACEs or limb-based events in patients with PAD (55).

1.5.1.2 Direct Oral Anticoagulants

An area of increased interest is the addition of direct oral anticoagulant (DOAC) agents to aspirin. DOAC are factor Xa inhibitors that act on the clotting cascade, therefore separate mechanism of action to antiplatelet agents. The recently published COMPASS trial (56) reported favourable reduction in MACE and limb-based complications with a combination of low dose rivaroxaban (2.5mg BD) and aspirin (150mg) compared to aspirin alone. The Voyager trial, solely designed to investigate

whether additional low dose rivaroxaban (2.5mg BD) is beneficial in patients with symptomatic PAD, observed an absolute risk reduction of 2.6% (HR0.85, 95%CI 0.75-0.95, p=0.009) in the composite endpoint (Acute limb ischaemia, major amputation, MI, CVA or death) at 3 years(57, 58). The vast majority of this additional benefit was in the prevention of limb or coronary thrombotic events. Both trials observed an increase in clinically significant bleeds in the combination therapy, possibly undermining the primary outcome benefits observed. There is some way to go before DOAC are routinely used in PAD patients who do not have indications for formal anticoagulation (atrial fibrillation, deep vein thrombosis and so on).

1.5.1.3 Statin therapy

Again, all guidelines concerning PAD recommend the use of high dose statin therapy in PAD patients. The area has been extensively researched in patients with PAD, it must be said that the majority of this research has been performed on patients with IC, however, it seems the results translate to the CLTI population. A Cochrane review which analysed 18 trials including >10,000 patients showed that 17/18 trials demonstrated significant benefit to statin therapy. The analysis calculated a significantly reduced risk of cardiovascular (mainly coronary) events in patients with PAD and statin therapy (Odds Ratio (OR), 0.74; CI 0.55-0.98) (59). The Heart Protection Study evaluated the effect of lipid lowering therapy on patients with PAD and included patients with CLTI (60). This trial randomised patient with blood LDL-Cholesterol of >3.5mmol/L (135mg/dL) to either Simvastatin 40mg OD (night) or placebo. They found a 25% relative risk (RR) reduction in major vascular events in patients with no history of coronary disease at baseline. Some evidence is now emerging that in those patients where statins are unsuccessful in reducing LDL-

Cholesterol to 70 mg/dL Ezetemibe (a fibrate which also lowers cholesterol) should be added (61) .

As well as targeting treatment to lowering cholesterol, statin therapy has been shown to reduce MACEs in patients with elevated systemic inflammatory markers, this association is poorly understood and is often referred to as the 'pleomorphic effects' of statins. The most robust research in this area is the JUPITER trial, who investigated primary prevention (rosuvastatin vs placebo) in patients with low LDL-cholesterol <3.5mmol/L but high levels of high sensitivity C-Reactive Protein. Patients receiving rosuvastatin had significantly (44%) reduced major vascular events and a 20% reduction in mortality (62). This effect seems to be consistent in reported case series whether there are smaller numbers (63) or large registry reports (64).

1.5.1.4 Antihypertensive treatment

Controlling patients high blood pressure (systolic BP <140mmHg and diastolic <90mmHg) has been shown to reduce MACEs in patients with PAD (65). Patients with PAD have significantly higher risk of MACE compared to those without (16.3% vs 9.2%). It has been found that controlling BP <145/90 mmHg reduces MACE (66), with further reduction if parameters were <130/80mmHg. Even lower levels (<120mmHg) had better freedom from MACE however these patients suffered more morbidity from hypotensive symptoms (67).

No consensus has been reached regarding first-line category for oral anti-hypertensive agent. In the UK, in non-black patients older than 55, Angiotensin Converting Enzyme inhibitors (ACEi) are recommended as first choice (68) (NICE CG127). Some concern has been expressed with ACEi as first line therapy in those patients with CLTI as some recent (non-randomised) literature has documented higher amputation events in

patients undergoing revascularisation for CLTI who take ACEi for blood pressure control (69, 70).

1.5.1.5 Type 2 Diabetes Mellitus

The majority of patients with PAD and DM have type 2 diabetes mellitus (T2DM), the majority of which will require pharmacological treatment to control the blood glucose. Current targets for blood glucose levels are a Hba1c of <7% (53mmol/mol). It is accepted in UK practise that Metformin monotherapy be initiated as the first line oral hypoglycaemic agent in patients with PAD. Palmer et al. published a large meta-analysis of 301 studies comparing differing oral hypoglycaemics in T2DM. They concluded that, of all the available agents, metformin had the lowest Hba1c levels and none conferred an advantage in terms of the primary endpoint of cardiovascular or all-cause mortality. Similarly, Metformin had the lowest rates (and therefore risk) of hypoglycaemia (71). It has been shown that metformin can increase the risk of contrast induced nephropathy, especially those with an estimated glomerular filtration rate (eGFR) of <30mL/min/1.73 m^2, it is therefore recommended that metformin be withheld immediately before and for 48 hours post infusion of contrast medium (72, 73).

1.5.1.6 Smoking cessation

In patients with PAD, despite optimal medical therapy, persistent smokers experience significantly higher rates of disease progression and MACEs (74). A sub-group analysis from the HOPE trial analysed MACEs in patients with stable/controlled cardiovascular disease or diabetes + 1 other risk factor. Of interest were those that did not change their smoking status during the trial period (4.5 years follow up). Active

smokers had a significantly increased relative risk of cardiovascular death (RR 1.65, 95% CI.28-2.14), MI (RR1.26, 95% CI 1.01-1.58), stroke (RR 1.42 (95% CI, 1.00-2.04) and all-cause mortality (RR 1.99, 95% CI 1.63-2.44). Interestingly, those patients who gave up smoking had a similar risk to that of non-smokers (75). The benefits of smoking cessation are observed in both men and women, to similar degrees, with reported reduction (for selective populations) in all-cause mortality of up to 30% (76).

1.5.2 Conservative Therapy

Conservative management of CLTI aims to modify risk factors and control pain. Currently all patients with PAD will be offered an antiplatelet (Clopidogrel 75 milligrams/day) and high dose statin therapy (Atorvastatin 80mg at night) along with modification of co-existing risk factors (DM, Hypertension, smoking cessation and obesity) (77) (NICE clinical guideline 181). Conservative treatment for CLTI has the worst clinical prognosis, with death or lower limb amputation quoted at >55% in one year (78, 79). In essence those patients treated with conservative management are often palliated.

1.5.3 Plain Balloon Angioplasty

PBA is the luminal treatment of PAD with specially designed non-conformable balloons (80-83). Early reports published promising results, at 1 year outcomes were broadly similar to OSB (84) and at 3 years limb salvage was approximately 49% (85). In this time period PBA was seen as an adjunctive procedure designed to supplement surgical bypass or for patients who were clinically unsuitable for bypass surgery.

Highly influential publications in the mid 1990's supported the primary use of PBA for revascularisation of patients with CLTI (86, 87). With feasibility established, and a

groundswell of enthusiasm (88), calls by academics were for a high quality RCT to address whether PBA was superior to OSB in patients with CLTI (89). Before an RCT could even be started large academic units had started moving to PBA first approach to CLTI (90) with acceptable results (12 months limb salvage of 76%).

The BASIL trial supported these observations in terms of limb-based outcomes, however those undergoing OSB lived longer within the trial (18, 91). The favourable results are still observed in more contemporary series (92, 93), with an ever increasing trend to an endovascular first strategy for treating CLTI. There has been no evidence generated that PBA is inferior to any other endovascular therapy (ET) and therefore NICE CG 147 (22) still recommend PBA as the first line endovascular intervention for CLTI.

1.5.4 Drug Eluting Technology

1.5.4.1 Drug Coated Balloon

The uptake of paclitaxel impregnated devices has been driven by a body of literature centred upon a comparison of DCB versus PBA (94-101). Here there have been many industry sponsored randomised controlled trials, some reporting 24-month patency 28.8% higher (INPACT SFA (98) than that of the PBA control arm. In fact, all of the randomised trials have reported superior rates of primary and primary assisted patency, target lesion revascularisation (TLR) and binary restenosis (BR) for DCB's. Despite the superior radiological outcomes none have shown a sustained significant improvement in walking distance, haemodynamic pressure to the foot (ABPI) or limb salvage. The most recent pooled meta-analysis of 9 randomised controlled trials including 1396 patients by Jongsma and colleagues confirms the above analysis.

They found DCB conferred a benefit over PBA for TLR (Risk Ratio (RR) 0.39, 95% CI 0.23-0.67) and BR (RR 0.37, 95% CI 0.23 – 0.58) at 12 months, this did not translate into clinical benefit at 12 months, concluding there was no difference in mean ABPI or Rutherford classification improvement, no difference in overall survival (RR 0.89, 95% CI 0.4 – 1.97) and freedom from amputation (RR 1.89, 95% CI 0.4 - 8.9)(102).

1.5.4.2 Drug Eluting Stent (DES)

The evidence base for drug DES is similar to that of DCB, only one major trial investigated stent versus PBA the ZILVER PTX trial (103), the rest compare DES with BMS (104, 105) or are in the infra-popliteal segment (106). Once again, the radiological results of the ZILVER PTX trial were overwhelmingly superior for the DES, primary assisted patency at 12 months was 83.1% vs 32.8% and freedom from TLR 90.5% vs 82.5%. However, no difference in clinical outcomes were observed; amputation 0% vs 0%, mean ABPI 0.91 vs 0.89, Rutherford class 0 - 44.7% vs 45.4% or improved walking distance 57.8% vs 57.7%. This was a reasonably large trial with 479 patients included but it must also be noted that 91% of these patients were suffering with intermittent claudication.

1.5.5 Other Endovascular Devices

Highly flexible bare metal stents designed for implantation into the lower limb arterial tree are becoming more popular especially in the treatment of CTO's. The most popular being the SUPERA stent, which has been found to be safe and effective with regard to clinically-driven target lesion revascularisation at 3 years in the SUPERB trial (107). Unfortunately, no direct comparison has been made with regard to PBA or OSB.

The three other areas of growth in endovascular devices are covered stents, bio-absorbable stents and percutaneous atherectomy (either laser, rotational, directional or orbital). Atherectomy is the most established of these treatments but again the same shortcomings in the evidence are apparent. There has been ease proving feasibility and immediate device safety (108-112), and larger series like the LACI registry reported encouraging short term outcomes in patients with poor surgical risk (ITS of 86% and a limb salvage of 92% at 6 months) it should be noted that 18% of the recruited patients had died prior to their 6 month follow up (113). Trials in this area are industry sponsored, trials are focused on the benefits of atherectomy versus PBA and are designed to show non-inferiority in radiological outcomes. A meta-analysis published in 2014 concluded there was no evidence that atherectomy conferred any benefit over PBA (114).

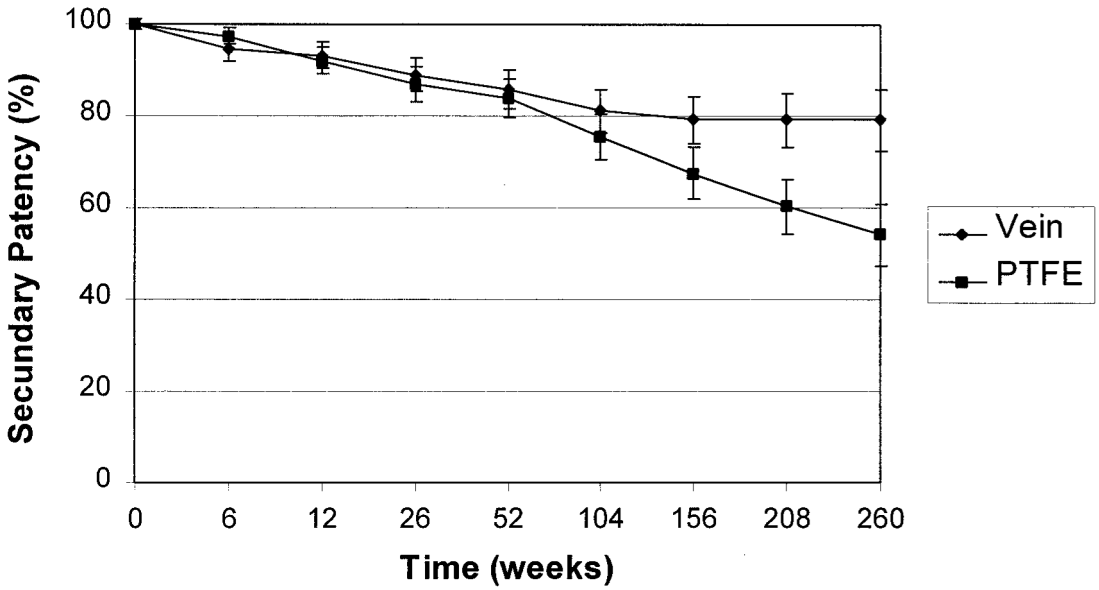
Covered stents are arterial stents scaffold with a non-stick material lining on the inner surface, the device that is most commonly deployed in the infra-inguinal arterial tree is the Viabahn (GORE). There is no high quality, independent RCT evidence to compare their clinical effectiveness against established treatments. The Viabahn stent has been more extensively used in the arterial tree, including iliac occlusive disease and as a visceral stent in complex endovascular aortic repair. With regard to safety in the infra-inguinal segment the VIASTAR trial concluded excellent primary patency rates at 12 months of 71% in TASC D lesions when compared to bare metal stenting (115). The Viabahn, in one retrospective clinical study, had similar three year patency rates to synthetic above-knee popliteal bypass (116), thus highlighting the reservations held by most vascular surgeons, these stents perform like synthetic bypass conduit – which do not perform well in the long term.

Very little data is available on bio-absorbable stents in the peripheral arteries. Most of what is reported is focused on cardiac stenting and the potential benefit of these stents alone or bonded with sirolimus. Certainly nothing to support their routine use in peripheral arterial disease.

1.5.6 Open Surgical Bypass

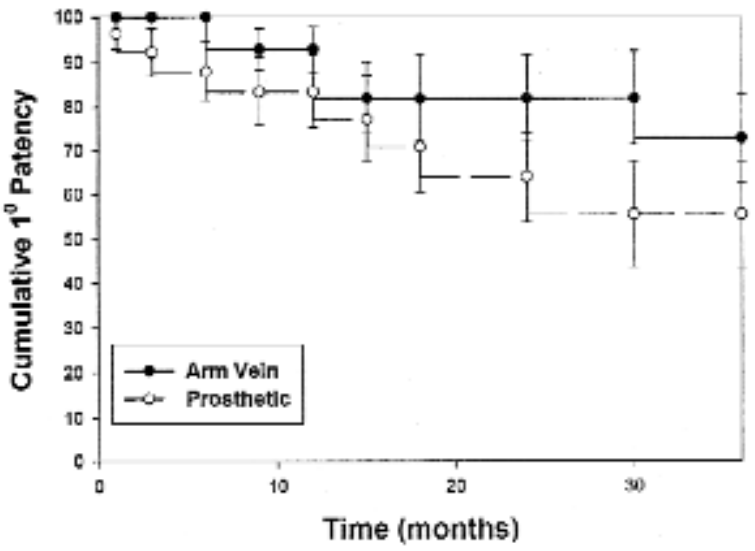
Lower limb bypass surgery using vein is the established gold-standard treatment for infra-inguinal revascularisation, especially in those patients suffering with CLTI. There is little evidence comparing bypass surgery versus other revascularisation techniques, however, some industry sponsored trials have been performed in an attempt to establish synthetic bypass conduit as a plausible alternative to autogenous vein. In all of the available literature GSV outperforms synthetic conduits in terms of patency whether the distal anastomosis is to the AK-pop artery (117-120), or the BK-pop artery (12, 121). Interestingly patency rates do not differ considerably for GSV if anastomosis is to the AK- pop (~80% at 5 years) or BK-pop (~75% at 4 years), and the same trend is observed for PTFE (AK-pop ~60%, BK-pop ~55%).

Fig 1.5.6.1 *Secondary patency rates over time comparing vein with polytetrafluoroethylene in above-knee femoro-popliteal bypass*



Enthusiasts for synthetic conduit have claimed that performing a vein cuff to the distal anastomosis (Miller cuff, St. Mary boot etc (122, 123)) improves graft patency, the evidence however does not support this stance, with no significant difference in patency in the popliteal artery (124, 125). Arm vein has also been studied where GSV is not available and found to have equivalent patency rates (although slight increase in graft related complications)(121).

Fig 1.5.6.2 *Life table analysis of variation in cumulative primary patency rates for femoro-below-knee grafts categorized by type of conduit. Arm vein grafts (solid line/solid circle) achieved significantly higher patency rates as compared with prosthetic grafts (dashed line/open circle)(121)*



When compared, it would seem that Dacron offers slight advantage in terms of patency compared to PTFE (126-130) and may even have better freedom from MALE (17.1% vs 30.7%)((128) although patency cannot be extrapolated to LS as the vast majority of patients studied had IC and therefore very low limb loss rates in all groups. Current practise therefore mandates the use of GSV wherever possible for performing OSB, if unavailable arm vein is an acceptable alternative and should be preferentially used over synthetic conduit. ET should be attempted (if possible) prior to electing to performing OSB with synthetic conduit due to the lower morbidity and improved performance. If the only conduit for revascularisation is synthetic, the evidence would support the preferential use of Dacron over PTFE.

Although there has been a global trend towards an endovascular first approach to managing patients with CLTI recent large case series have questioned the

appropriateness of this and maintain that bypass surgery remains the best option in this challenging cohort (131, 132).

1.5.7 Major Lower Limb Amputation

Primary amputation is often used for patients with unsalvageable tissue loss, sepsis in the limb threatening life, or pain secondary to ischaemia that cannot be improved or managed medically. Depending on the level of arterial occlusion primary amputation may be BKA,TKA or AKA. Historically overall survival after major amputation for CLTI was quoted as 50% at 1 year. A recent analysis in one centre of elderly patients (>70 years) undergoing MLLA, reported a mortality of 44% and 85% at 1 and 3 years respectively (133). There has been a very hard drive to improve these outcomes in the UK since the publication of the national confidential enquiry into patients outcomes and death (NCEPOD) report into Major amputations(134). The Health Quality Improvement Partnership (HQIP) set out a number of standards of care in an aim of improving outcomes in MLLA, including, consultant vascular surgeon and vascular anaesthetist presence in theatre, MLLA to be performed on elective vascular surgery list, optimisation of modifiable risk factors (hypertension, DM), strategies for post procedural pain and dedicated MLLA physiotherapy. Ultimately understanding the co-morbid status of the patient requiring MLLA is likely to have the biggest impact on survival and HRQL post MLLA (34).

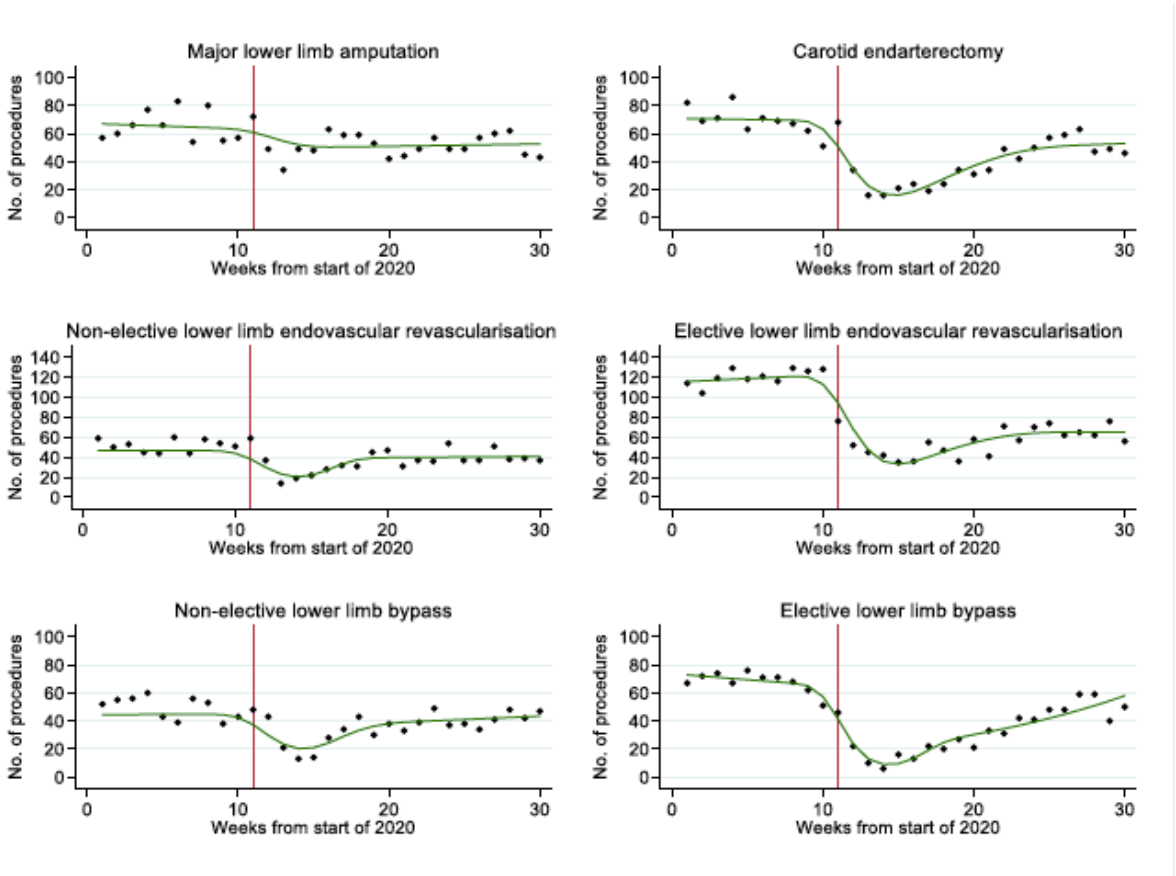
1.5.9 Cost effectiveness

Unfortunately, BASIL is the only trial to provide health economic data exclusively for patients with CLI. BASIL provided cost effectiveness analysis to compare a bypass first with angioplasty first strategy for CLTI. At 12 months (to include re-admissions and re-interventions) bypass first was $5,521 more expensive than angioplasty first ($45,322 for BSX vs $39,801 for BAP). They concluded that an incremental cost effectiveness ratio (ICER) for a bypass first strategy was $184,492 (135). Some of the endovascular device trials mentioned earlier, do provide a health economics analysis, but as these are mainly trials on patients with IC the same outcomes cannot be associated with CLTI reliably. One of the more difficult, but important points to establish is the baseline health economic impact of primary amputation. CLTI interventions should be compared against this baseline as well as each other. Because primary amputation is very costly (in terms of rehabilitation and social care costs), it is exceedingly likely that all interventions that are available are cost effective in comparison, but for low and middle-income countries as well as those nationally funded health systems it is important to know which treatment offers the best value for money for the system as a whole.

1.6 SEVERE ACUTE RESPIRATORY SYNDROME – CORONAVIRUS DISEASE - 2 (COVID-19)

In 2019 a new viral infection was detected in the Wuhan province of China, by March 2020 this had spread to the UK and soon after was declared a pandemic. The consequences of this infection were profound, not only on those infected with the virus prior to vaccination (severe acute respiratory syndrome (SARS), hospital admission, intensive care unit care and Death) but on the whole population. During lockdown the whole focus of the UK NHS was on creating capacity for the oncoming surge of patients. Patients with all other illnesses were expedited from hospitals to 'places of safety'. Admission of any condition that was not COVID-19 were avoided at all costs, and interestingly there was a vast reduction in patients attending healthcare settings with myocardial infarction, cerebrovascular accident, transient ischaemic attack and CLTI (136). In terms of vascular surgery, it was clear that those patients infected with COVID-19 were experiencing significant intra-arterial thrombosis, however, patients requiring vascular surgery who had active COVID-19 had an exceedingly poor prognosis (at least initially). In April 2020 (NVR report) reported activity on the national vascular registry (NVR) had dropped to 12% of that expected, but had returned to approximately 80% by July 2020 (with marked regional variation).

Figure 1.6.1 *Weekly number of lower limb procedures and Carotid endarterectomies in NHS vascular units between 1Jan - 1 Aug 2020 by type of procedure (NVR report, Nov 2020)*



The activity of vascular centres has not yet returned to pre-pandemic levels, prompting questions as to whether established referral practices are no longer appropriate and whether patient engagement with health care is more hesitant as hospitals are seen as places where the risk of nosocomial COVID-19 infection are high. There may also be restrictions on availability of clinics/operating theatres and inpatient space as the NHS struggles to re-establish the services it once provided pre-pandemic. As well as the impact on infrastructure and patients, COVID-19 has had a significant impact on the training of Vascular Surgeons in the UK. Most trainees have performed far fewer

procedures across the spectrum of vascular surgery but have also had reduced exposure to emergency admissions and decision making as well as outpatient consultations.

1.7 SUMMARY

Given that CLTI is a well-recognised health problem, the dearth of high-quality evidence addressing the subject is suprising. In terms of best medical therapy, there are hundreds of studies, mainly in patients with either cardiac or cerebrovascular disease with concomitant PAD. The benefits for antiplatelet and statin therapy in terms of limb outcomes are not well studied (although there does seem to be an additive effect in the VOYAGER trial) there is overwhelming evidence supporting their use for secondary prevention of cardiac and cerebrovascular events in the PAD population. This too is true for controlling HTN and DM and for the cessation of smoking. In terms of treatment of patients with CLTI the water is far muddier. Treatment options remain varied, in terms of which to choose first, OSB or ET. Within these specific disciplines there are many different techniques or devices which are all deployed according to surgeon preference and availability. The reason for this must be a lack of stratification at the patient level; for instance, we are still unable to predict accurately which patients are low, medium and high risk for surgical intervention. Neither do we fully understand the varying physiological demands from the different presentations of CLTI (rest pain, compared to shallow ulceration, gangrene or even osteomyelitis). Finally, due to the varied anatomy of disease suffered by most patients (almost all patients will be suffering with at least two-level disease) it has been a challenge to even define the likelihood of ITS with different treatments let alone their long-term durability. All of these factors contribute in varying quantities to whether patients will experience successful and prolonged treatment for their CLTI. The GVG have started the process of addressing these issues. They have recommended the use of the WIfI score in an attempt to understand the degree of limb threat at presentation (and subsequently) by

quantifying the degree of ischaemia (ABPI), tissue loss (depth and are of tissue damage) and the degree of local and systemic infection. Although this system requires refinement, it would seem that it is informative in terms of indicating the degree of limb threat for patients. It would also seem that it may also differentiate those patients who are likely to improve with endovascular treatment versus those who require bypass surgery (higher WIfI score). The GLASS score attempts to address patterns of anatomy and predict success of ET. Used in combination with WIfI it will help direct type of treatment provided; for instance in those with moderate limb threat (by WIfI (2-3)), endovascular treatment would likely be sufficient, but if their disease is GLASS 3 then endovascular intervention is not likely to be successful past 1 year, which may persuade the patient and the clinician to opt for OSB instead.

In terms of open versus endovascular intervention we only have BASIL-1 to guide us, their recommendation from nearly 20 years ago was to perform vein bypass surgery for patients with CLTI expected to live longer than two years (in patients where there is equipoise between the two treatments). In terms of endovascular intervention, it seemed that the advancement in technology (the introduction of paclitaxel coated devices) was going to bring a new horizon to the treatment of patients with CLTI. Unfortunately, these patients have not been studied and with the publication of Katsanos meta-analysis in 2018 and 2020 indicating questions over negative effects on long term survival with these devices, as well as their much increased cost, it would seem there has been no genuine progress in advancing treatment of CLTI since BASIL-1.

There is some hope, currently BASIL -2, BASIL-3 are all in the follow up phase of their trials and BEST CLI have recently reported their first results. Each are WIfI and

GLASS scoring their patient cohort to help validate these tools and provide data to further refine them. They will also provide clinical and health economic data on the treatments of infra-popliteal disease, the role of drug eluting stents and drug coated balloons in the femoro-popliteal segment as well as a comparison with synthetic graft material (BEST-CLI). Along with the individual trials, the trialists have agreed to perform an individual patient data meta-analysis in the hope of providing definitive answers to the questions being addressed.

Regarding femoro-popliteal (FP) revascularisation there are large omissions in the literature supporting current trends in treatment. This thesis will attempt to answer many of the questions regarding optimal treatment for FP disease.

1.8 ACKNOWLEDGMENT OF COLLABORATIVE AUTHORS

Chapter 3.1 co-authors:

Mr Gareth Bate	Lead research nurse for the BASIL trials. Provided access to data and supported data extraction
Mrs Smitaa Patel	Provided statistical advice and support
Professor Andrew Bradbury	Senior author, overall responsibility

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Chapter 3.3 co-authors:

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Mr Huw Davies	Assisted with study design and critical appraisal of final manuscript
Dr Akio Kodama	Assisted with study design and critical appraisal of final manuscript
Dr Michael Conte	Assisted with study design and critical appraisal of final manuscript
Professor Andrew Bradbury	Senior author, overall responsibility

2 METHODOLOGY

2.1 BYPASS VERSUS ANGIOPLASTY FOR SEVERE ISCHAEMIA OF THE LIMB (BASIL) TRIAL (HTA PROJECT 96/05/01) – BASIL-1

The original BASIL trial, contemporarily known as BASIL-1, recruited 452 patients between August 1999 and June 2004. Patients underwent a minimum 2-year follow-up but many were followed up far longer due to the slower than anticipated recruitment. Participating centres (N=27) were invited to recruit all patients presenting with rest/night pain or tissue loss as a result of infra-inguinal atherosclerotic disease and were deemed suitable by a consultant surgeon and radiologist to undergo bypass surgery or angioplasty. The study was approved by the Multi-centre Research Ethics Committee for Scotland, ISRCTN45298889. Patients were randomised to either a 'bypass-first' or 'balloon angioplasty-first' revascularisation strategy. Randomisation was performed on a one-to-one basis via predetermined sealed envelopes. Randomisation was stratified by centre and then by clinical presentation and ankle pressure.

With regards to intervention, centres were encouraged to perform the randomised intervention as soon as possible, they were permitted to use their normal practise with regard to pre-intervention assessment and treatment. Centres were allowed to use the devices they would normally use in their current practise and with regard to bypass surgery any conduit was permitted. Any secondary interventions were left to the judgement of the responsible clinician. Clinical follow up was not prescriptive, centres were allowed to follow up patients along their normal pathways, neither was there any

requirement to perform routine ultrasound surveillance if this was not the standard practise. Patients underwent trial based follow up at 1, 3, 6, 12 months and yearly thereafter. Primary clinical outcome was AFS, with many other important clinical outcomes reported (all-cause mortality, LS and FFR).

As part of this thesis, the original BASIL cohort will undergo subgroup analysis of patients undergoing femoro-popliteal interventions to provide a historic baseline of outcomes for patients undergoing surgical bypass and best endovascular therapy for CLTI. Patient selection will be performed to comply with the inclusion criteria for BASIL-3; CLTI thought to be predominantly due to FP +/- IP disease. Primary outcome will be AFS, secondary outcomes will include OS, LS, FFR, MALE as well as 30 day post procedural complications and morbidities. All available demographics will be analysed to quantify differences in patient baseline characteristics prior to intervention.

2.2 CONTEMPORARY SERIES

A contemporary series of patients with CLTI undergoing FP angioplasty or FP bypass surgery performed between 2009-2014 (ten years on from BASIL) in one academic vascular unit (Heart of England Foundation Trust (HEFT)) will be used as a contemporary reference for outcomes of revascularisation. Patients will be selected based on the inclusion criteria to the BASIL-3 trial:

- CLTI due to primarily FP disease (IP interventions at same sitting permitted)
- No intervention to the target artery in the previous 12 months of the index procedure
- If bilateral disease, only first eligible limb included

These patients will be identified using local hospital episode statistics (HES) and for patients undergoing endovascular intervention; searching the radiology CRIS system. Patients undergoing surgical intervention will also be identified manually from theatre log-books. These will then be cross checked with the prospectively maintained hospital electronic patient record (Concerto) to ensure the patients meet the inclusion criteria. This electronic database will also be interrogated for baseline demographic and clinical outcome data.

Outcomes will be broadly similar to that reported for the BASIL cohort. Primary outcome will be amputation free survival (AFS), secondary outcomes will include overall survival (OS), limb salvage (LS), freedom from re-intervention (FFR), major adverse limb events (MALE) as well as 30 day post procedural complications and morbidities. All available demographics will be analysed to quantify differences in patient baseline characteristics prior to intervention.

2.3 NATIONAL VASCULAR REGISTRY

Currently the national vascular registry (NVR) in the UK requires all patients undergoing aortic, carotid, lower limb bypass, lower limb angioplasty and amputations to be entered into the database. Historically the compliance has been poor, however since the publication of individual surgeon outcomes in 2013 individual and unit co-operation with data capture has exponentially increased. The NVR records baseline demographic data, procedural data, inpatient outcome data and outcome data up to first follow up appointment. Although short term outcome is of limited value in PAD, especially in CLTI, it does give an accurate assessment of individual and organisation procedural safety and is a reliable source of patient data for the purposes of analysing

individual hospital activity and outcomes. Within this thesis, the NVR has been used to check accuracy of procedure details as well as patient demographics and short term clinical outcomes.

2.4 RADIOLOGICAL SCORING

2.4.1 Bollinger Score

The Bollinger score is a highly effective way of quantifying the burden of arterial disease, however, is time consuming, operator dependent and is of little value in the clinical setting. In an attempt to help stratify the patients included in this thesis, Bollinger Scores are provided for BASIL-1 patients and those patients in the CS. Scores were calculated if the patient had Magnetic Resonance Angiogram (MRA), Computed Tomography Angiogram (CTA) or Digital Subtraction Angiogram (DSA). For Iliac, femoral and popliteal vessels quantification of disease will be equivalent between all three modalities, for the crural (PT, AT, PP) vessels, DSA provides the most accurate images with CTA providing the most difficult to interpret. For the purpose of this work, the crural vessels were scored regardless of the modality, however it must be accepted that there is a potential compromise in the accuracy of IP scores.

With regards to the figures provided for comparison, as previously described Bollinger scores each arterial segment in two sections. In previous publications, a mean arterial segment value is provided for comparison. For the purpose of this work, some chapters will provide combined scores to mimic what is considered in clinical decision making. For instance, Femoro-popliteal (FP) score. This is a cumulative score for the

femoro popliteal segment i.e. PFA +SFA1+SFA2+Pop1+Pop2=FP score. Again, the infra-popliteal score is provided as a cumulative score of all the crural vessels. These figures allow us to understand the amount of disease that must be overcome if a patient is undergoing endovascular intervention, and if undergoing surgical bypass, allows us to understand the quality of the run-off.

2.4.2 GLASS Score

As previously described, the GLASS score is a newly formulated anatomical staging system devised by the GVG in an attempt to provide some structure to the decision making in revascularisation of the limb based on the disease anatomy. This score considers vessels in thirds, providing a FP grade of disease and IP grade of disease. Although un-validated, this system provides us with another method of validating burden of disease in included patients. It also allows us to assess whether burden of disease is different within groups and therefore maybe a significant factor in any differing results. Conveniently the consideration of the FP and IP segment separately allows for direct comparison with Bollinger. The pedal modifier wasn't used in this work as the number of reliable images were low with much uncertainty as to how reliable this section can be scored using CTA/MRA.

For the purpose of this work, individuals were scored if they had a CTA, MRA or DSA for evaluation, accepting the limitations described with the Bollinger score. It is important to note that the GLASS score should be increased by 1 if there is significant calcification. It is difficult to determine this if patients only have MRA/DSA for evaluation, which may affect some of the patients included.

2.5 STATISTICS

Time to event analyses up to a 7-year period using Kaplan-Meier plots are provided for the historic analyses. Hazard ratios were used to detect statistically important differences in outcomes using a 95% confidence interval. Differences between the groups were compared using t-test, χ^2-squared and Wilcoxon Rank Sum tests according to distribution of data using SAS v9.4 and SPSS v24.

3 RESULTS

OVERVIEW

Section 3.1 and 3.2 are subgroup analyses of the original BASIL trial. Section 3.1 explores the clinical outcomes for patients undergoing either OSB or PBA +/- BMS to the FP segment, setting the baseline expectations for more contemporary results.

Section 3.2 investigates whether patients undergoing ET first who required secondary bypass within the BASIL trial had comparable outcomes to those patients undergoing primary OSB.

Section 3.3 and 3.4 compare a contemporary series of patients with CLTI undergoing FP intervention against those patients in the BASIL trial. Section 3.3 compares those patients who underwent primary ET for FP disease between 2009-2014 versus those patients randomised to endo in the BASIL trial. Section 3.4 compares patients undergoing primary OSB to the FP segment between 2009-2014 to those undergoing similar interventions in the BASIL trial.

Section 3.5 compares the clinical outcomes of those patients with CLTI who had ET first or OSB first for FP induced CLTI in a contemporary series between 2009-2014.

Section 3.6 uses an IP and FP contemporary series undergoing endovascular intervention from 2009-2014 to assess the predictive accuracy of the GVG GLASS score for ITS and whether that correlates with clinical outcomes.

3.1 A COMPARISON OF CINICAL OUTCOMES FOLLOWING FEMORO-POPLITEAL BYPASS OR PLAIN BALLOON ANGIOPLASTY WITH SELECTIVE BARE METAL STENTING IN THE BYPASS VERSUS ANGIOPLASTY IN SEVERE ISCHAEMIA OF THE LIMB (BASIL) TRIAL

ABSTRACT

Objective

To compare outcomes in patients with chronic limb threatening ischaemia (CLTI) due to femoro-popliteal (FP), with or without infra-popliteal (IP), disease who underwent FP (vein or synthetic) open surgical bypass (OSB) or plain balloon angioplasty (PBA), with or without bare metal stenting (BMS), in the Bypass versus Angioplasty in Severe Ischaemia of the Limb (BASIL-1) trial.

Method

Data were extracted from BASIL-1 case record forms. Outcomes reported include immediate technical success, freedom from major adverse limb events (FF-MALE) and further re-intervention (FF-R), amputation free survival (AFS), overall survival (OS), and limb salvage (LS).

Results

Patients underwent primary OSB (n = 128; 89 vein, 39 synthetic) or primary PBA (n = 183; 6 had BMS). Mean follow-up was 46.2 and 43.6 months respectively. Patients were well matched at baseline except that PBA +/- BMS patients were significantly more likely to be current smokers. There was no difference in overall or IP (run-off) Bollinger angiogram scores between groups. Immediate technical success was significantly higher for OSB (98% vs. 81%, $p<0.0001$). OSB was associated with a

longer mean index hospital admission (p=0.001) but there was no difference in hospital days at 12 months. FF-MALE (HR 1.51, p=0.04) and FF-R (HR=1.68, p=0.02), but not AFS (HR 1.18, p=0.4), OS (HR 1.14, p=0.5) and LS (HR 1.09, p=0.8) were significantly better following OSB.

Conclusion

Although AFS, OS and LS were similar in the two groups, OSB was associated with significantly fewer MALE and re-interventions. So, while PBA +/- BMS may be a less resource intensive (expensive) and morbid option in the short term, this appears unlikely to be the case in the longer term. Present data add further weight to the argument that, where possible, patients presenting with CLTI due to FP disease should be offered OSB as their primary revascularisation procedure.

INTRODUCTION

The Bypass versus Angioplasty for Severe Ischaemia of the Leg trial, now known as the BASIL-1 trial, remains the only published randomised controlled trial (RCT) to have compared an open surgical bypass (OSB) first, with a plain balloon angioplasty, with or without bare metal stenting, (PBA +/- BMS) first revascularisation strategy for chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease (18, 21). In BASIL-1, approximately 75% of patients had predominantly femoro-popliteal (FP) disease and intervention while in about 25% the disease and intervention were predominantly infra-popliteal (IP). A recently published BASIL-1 IP sub-group analysis showed that, when compared to PBA (no IP BMS were used), a vein bypass (VB) first strategy resulted in better overall survival (OS), amputation-free survival (AFS), and quality of revascularisation (time to wound healing and relief of ischaemic rest pain)(20). Despite BASIL-1, the only currently available 'level 1' evidence, showing better long-term clinical outcomes following OSB, there has nevertheless been a non-evidence-based trend towards offering primary endovascular intervention to patients with CLTI due to FP disease. The aim of this BASIL-1 sub-group analysis, therefore, is to compare outcomes in patients who underwent FP OSB (VB and synthetic, SynB) or PBA +/- BMS as their primary revascularisation procedure

METHODS

BASIL-1 trial

BASIL-1 methods and ethical approvals have been published previously(137). In brief, between August 1999 and June 2004, 452 patients with CLTI due to infra-inguinal disease were randomised to an OSB first or a PBA +/- BMS first revascularisation

strategy. Patients were eligible for trial inclusion if the responsible clinicians felt that they required early revascularisation and were in clinical equipoise OSB and PBA +/- BMS. Patients were followed up by six dedicated research nurses at 1, 3, 6, and 12 months post randomisation and then annually until death or 1 July 2007. The primary endpoint was amputation free survival (AFS) and secondary end-points included overall survival (OS), limb salvage (LS) and requirement for re-intervention. BASIL-1 was a multi-centre, pragmatic, clinical effectiveness RCT that allowed participating units to continue to use their preferred post-intervention surveillance programmes. However, the majority of the re-interventions were due to persisting or recurrent symptoms and signs of CLTI.

Inclusion criteria for FP subgroup analysis

In order to be included in the current sub-group analysis, BASIL-1 patients had to fulfil two criteria. Firstly, they had to have atherosclerotic FP disease causing CLTI and, secondly, they only underwent intervention to the FP segment (with no IP intervention). Baseline and clinical outcome data were extracted from the original prospectively gathered BASIL-1 case record forms.

Outcomes

In this BASIL-1 FP sub-group analysis, we report immediate technical success (as defined by the operating surgeon or interventionalist), mean length of index hospital admission, days spent in hospital out to 12 months from randomisation, freedom from major adverse limb events (FF-MALE) and re-intervention (FF-R), AFS, OS, and LS. Major amputation was classified as amputation of the trial limb above the ankle. We have chosen not to include minor amputation as a re-intervention as we regard this as being mainly determined by the condition of the foot at presentation and not the type of primary revascularisation. Major adverse limb event (MALE) comprised any

revascularisation attempt or major amputation of the trial limb during follow up. Post-procedural complications are reported as 30-day mortality, morbidity (complications and re-interventions) and major adverse cardiovascular event (MACE) which comprises death, myocardial infarction or cerebrovascular event. Unplanned interventions for post-operative complications, revascularisation (OSB or PBA +/- BMS), or major amputation were collated and reported under the term surgical re-interventions if they occurred within 30-days. No patients were lost to follow up for the primary endpoint or the other secondary endpoints reported here. Patients who partially withdrew had their clinical outcome data collected via UK centralised data-bases, now known as ONS (office of national statistics) and HES (hospital episode statistics) data.

Statistics

Time to event analyses comparing all OSB (VB and SynB) with PBA +/- BMS are presented over a 7-year period using Kaplan-Meier plots and Log-Rank test for significance. Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the groups were compared using t-test, χ^2-squared and Wilcoxon Rank Sum tests according to distribution of data using SAS v9.4.

RESULTS

Demographics

There were 311 patients; 128 underwent primary OSB (89 VB, 39 SynB) and 183 had primary PBA +/- BMS (6 stents). The mean follow-up was 46.2 (range 0-91) and 43.6 (range 0-93) months respectively. Ipsilateral great saphenous vein (GSV) was used for 83 (93%) VB; arm vein was used for 1 (1%) and composite vein (arm and leg vein spliced) for 5 (6%). Most VB were reversed (63, 71%) with (23, 26%) being in-situ and (3, 4%) non-reversed. The two groups were very similar in terms of baseline characteristics although PBA +/- BMS patients were more likely to be current smokers, and there was a trend to more chronic obstructive pulmonary disease (COPD) in OSB patients (**Table 3.1.1**).

Distribution of Disease

There was no significant difference in the overall burden of disease between the two groups in terms of Bollinger angiographic scores (p = 0.2) (**Table 3.1.2**). IP disease severity was also statistically similar in the two groups (Bollinger Score = 44.4 vs 46.6, p=0.4) with the peroneal artery being the least diseased run-off vessel.

Table 3.1.1 *Baseline characteristics in patients undergoing open surgical bypass and plain balloon angioplasty +/- bare metal stent*

		OSB (n = 128)	PBA +/- BMS (n = 183)	P Value
Conduit	Vein	89 (70%)	-	
	Synthetic	39 (30%)	-	
	PBA+/-BMS	-	183 (100%)	
Gender	Male	78 (61%)	94 (51%)	0.09
Limb	Right	57 (45%)	75 (41%)	0.5
Age	Mean (SD)	71.7 (8.0)	73.1 (8.6)	0.2
Follow up (months)	Mean (SD)	46.2 (27.2)	43.6 (24.7)	0.4
Indication	Rest pain	52 (41%)	69 (38%)	0.4
	Tissue Loss	14 (11%)	14 (8%)	
	Both	62 (48%)	100 (54%)	
Creatinine	Mean (SD)	111.7 (79.4)	107.7 (60.2)	0.6
Smoker	Never	17 (13%)	36 (20%)	0.04
	Ex-Smoker	65 (51%)	67 (36%)	
	Current	46 (36%)	80 (44%)	
Diabetes Mellitus		47 (37%)	74 (40%)	0.5
Congestive Heart Failure		5 (4%)	8 (4%)	0.8
Hypertension		77 (60%)	108 (59%)	0.8
Coronary Artery Disease		35 (27%)	50 (27%)	1.0
Chronic Obstructive Airway Disease		19 (15%)	15 (8%)	0.06

OSB - Open Surgical Bypass

PBA - Plain Balloon Angioplasty

BMS - Bare Metal Stent

Table 3.1.2 *A comparison of Bollinger scores between open surgical bypass and plain balloon angioplasty +/- bare metal stent groups*

Arterial Section	OSB (n = 128)	PBA+/-BMS (n = 183)	P Value
Profunda Femoris	1.6 (2.6)	2.1 (3.4)	0.2
Proximal Superficial Femoral	7.0 (5.9)	7.0 (5.5)	0.9
Distal Superficial Femoral	10.3 (4.9)	10.2 (5.0)	0.8
Proximal Popliteal	6.9 (5.8)	7.1 (5.7)	0.7
Distal Popliteal	1.5 (2.5)	2.7 (4.4)	0.007
Tibio-peroneal Trunk	2.5 (3.6)	2.8 (4.3)	0.6
Proximal Posterior Tibial	6.8 (5.9)	8.2 (6.6)	0.05
Distal Posterior Tibial	8.3 (6.6)	9.3 (6.5)	0.1
Proximal Peroneal	4.4 (4.8)	4.6 (5.2)	0.7
Distal Peroneal	5.8 (6.2)	4.5 (5.6)	0.1
Proximal Anterior Tibial	6.0 (6.1)	5.8 (5.7)	0.8
Distal Anterior Tibial	7.2 (6.8)	6.7 (6.6)	0.6
Plantar	6.7 (4.0)	6.5 (4.4)	0.8
Total	70.7 (24.5)	75.1 (27.3)	0.2
Total Infra-popliteal Score	44.4 (22.4)	46.6 (24.1)	0.4

OSB - Open Surgical Bypass
PBA - Plain Balloon Angioplasty
BMS - Mare Metal Stent

Short-term outcomes

Immediate technical success was highly significantly better for OSB (98% vs. 81%, p<0.0001). Although patients undergoing OSB had a longer median (inter-quartile range, IQR) index hospital admission (16 [10-27] vs. 8 [2-19] days, p=0.0001) by 12 months patients in both groups had spent an equivalent median (range) number of days (17 [11-28] vs 17 [6-41], p=0.7) in hospital. Statin use was low in both groups (OSB 30% vs. PBA +/- BMS 37%, p=0.2). Antiplatelet use was significantly higher in OSB patients (66% vs. 55% p=0.05). Although all-cause 30-day mortality was not statistically different between the two groups, OSB patients suffered more morbidity; in particular, wound infection (**Table 3.1.3.**). PBA +/- BMS patients required more surgical interventions within the first 30-days (2% vs. 7%, p=0.06).

Table 3.1.3 *Morbidity and mortality (30 day) in patients undergoing open surgical bypass and plain balloon angioplasty +/- bare metal stent*

	OSB (n = 128)	**PBA+/-BMS (n = 183)**	**P Value**
Mortality (30 days)	7 (5%)	6 (3%)	0.3
Morbidity and mortality (30 days)	58 (45%)	59 (32%)	0.02
Myocardial infarction	5 (4%)	5 (3%)	0.6
Transient ischaemic attack	0 (-)	2 (1%)	0.2
Cerebrovascular accident	1 (1%)	3 (2%)	0.5
Haematoma (not operated)	7 (5%)	8 (4%)	0.7
Haematoma (operated)	2 (2%)	1 (1%)	0.4
Wound Infection	37 (29%)	29 (16%)	0.006
Lower respiratory tract infection	4 (3%)	5 (3%)	0.8
Urinary tract infection	2 (2%)	3 (2%)	1.0

False Aneurysm (not operated)	1 (1%)	0 (-)	0.2
False Aneurysm (operated)	0 (-)	0 (-)	-
Major Amputation	3 (2%)	9 (5%)	0.3
Surgical Intervention (30 days)	3 (2%)	13 (7%)	0.06
Major adverse cardiovascular event	10 (8%)	10 (5%)	0.4

OSB - Open Surgical Bypass
PBA - Plain Balloon Angioplasty
BMS - Bare Metal Stent
*Wound Infection includes foot infection as well as infection at the intervention site

Long term clinical outcomes OSB vs PBA+/-BMS

There was no difference in AFS (62% vs. 55%, HR 1.18, 95% CI 0.82-1.69, p=0.4) (**Figure 3.1.1**), OS (69% vs. 63%, HR 1.14, 95% CI 0.77-1.70, p=0.5) (**Figure 3.1.2**) or LS (85% vs. 85%, HR 1.09, 95% CI 0.59-2.01, p=0.8) between OSB and PBA+/-BMS. However, FF-MALE (67% vs. 56%, HR 1.51, 95% CI 1.01–2.25, p=0.04) (**Figure 3.1.3**) and FF-R (72% vs. 63%, HR=1.68, 95% CI: 1.09–2.60, p=0.02) (**Figure 3.1.4**) were significantly lower following OSB. Resolution of rest pain (85% vs 76%, HR=0.84, 95%CI 0.63–1.11 p=0.2) and wound healing at 3 years (90% vs 84%, HR=0.78, 95%CI 0.55-1.10 p= 0.2) (**Figure 3.1.5**) were similar in the two groups.

Figure 3.1.1 *Cumulative Kaplan Meier estimate of amputation free survival in patients undergoing femoro-popliteal (FP) bypass and plain balloon angioplasty +/- bare metal stent (PBA+/-BMS) in the BASIL-1 trial*

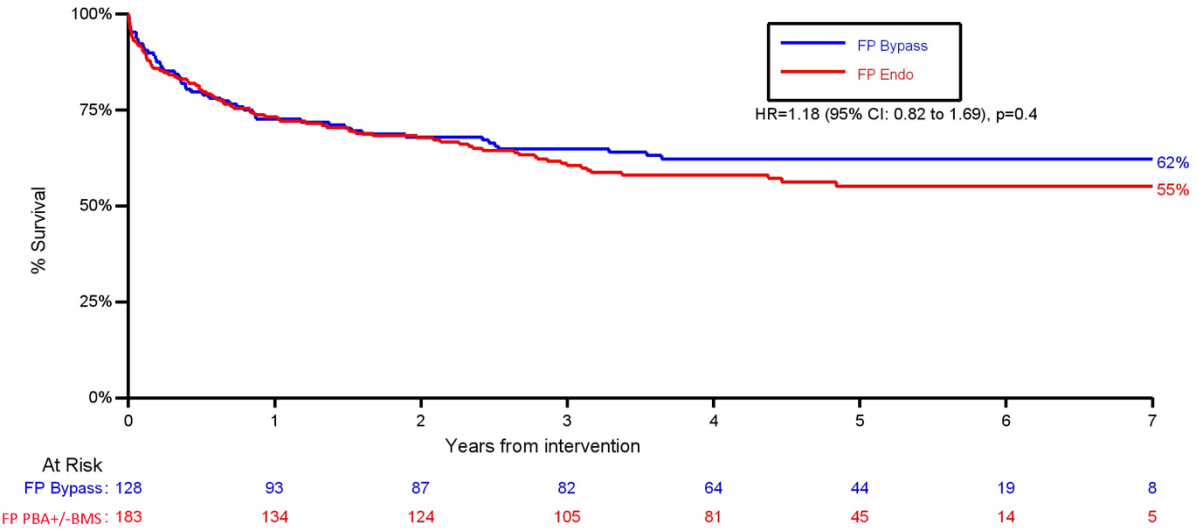


Figure 3.1.2 *Cumulative Kaplan Meier estimate of overall survival in patients undergoing femoro-popliteal (FP) bypass and plain balloon angioplasty +/- bare metal stent (PBA+/-BMS) in the BASIL-1 trial*

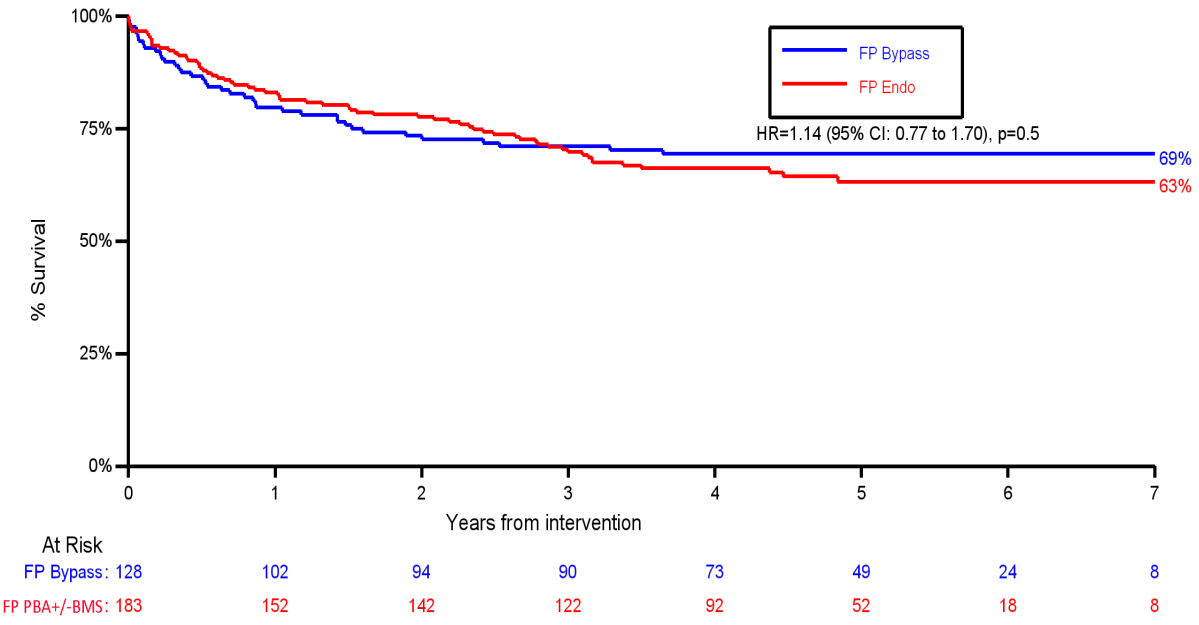


Figure 3.1.3 *Cumulative Kaplan Meier estimate of freedom from major adverse limb events in patients undergoing femoro-popliteal (FP) bypass and plain balloon angioplasty +/- bare metal stent (PBA+/-BMS) in the BASIL-1 trial*

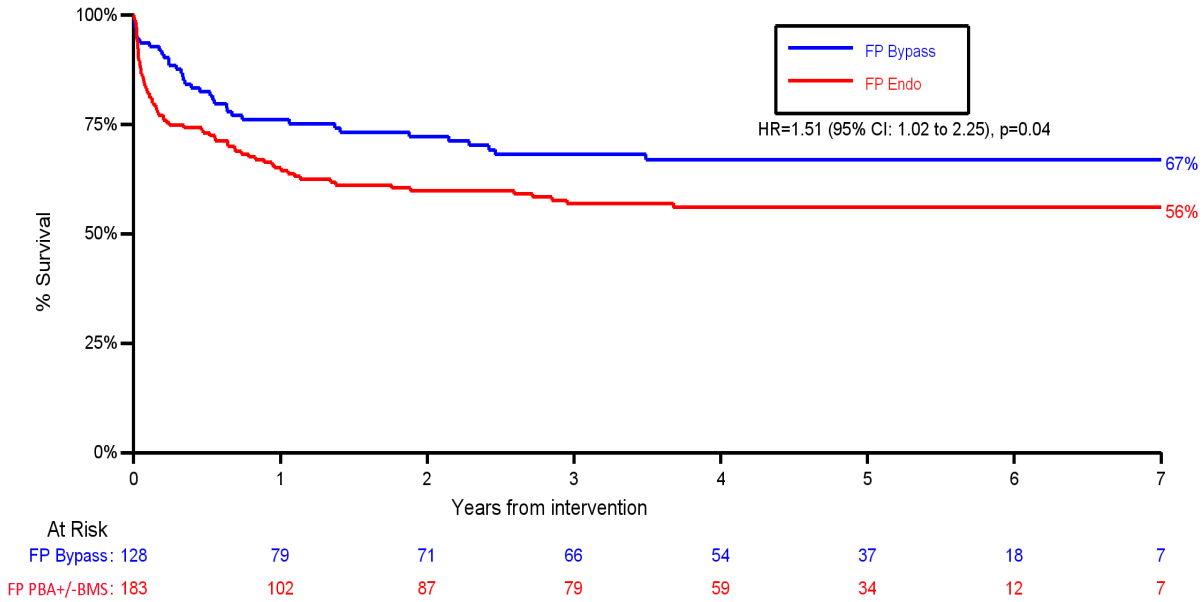


Figure 3.1.4 *Cumulative Kaplan Meier estimate of Freedom from re-intervention in patients undergoing (FP) bypass and plain balloon angioplasty +/- bare metal stent (PBA+/-BMS in the BASIL-1 trial*

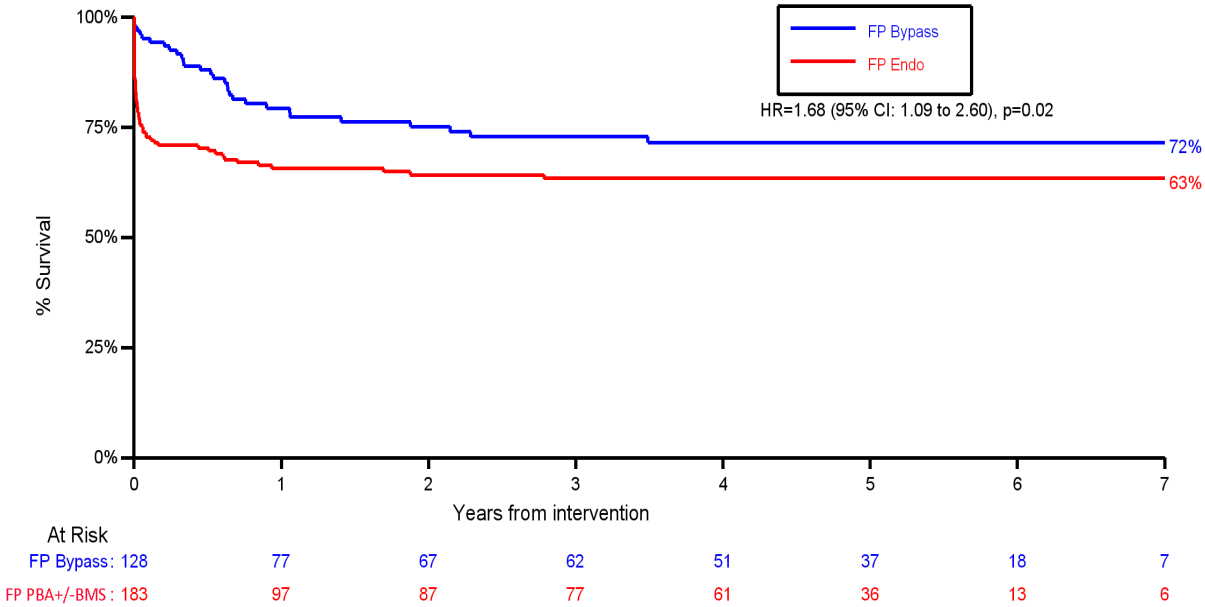
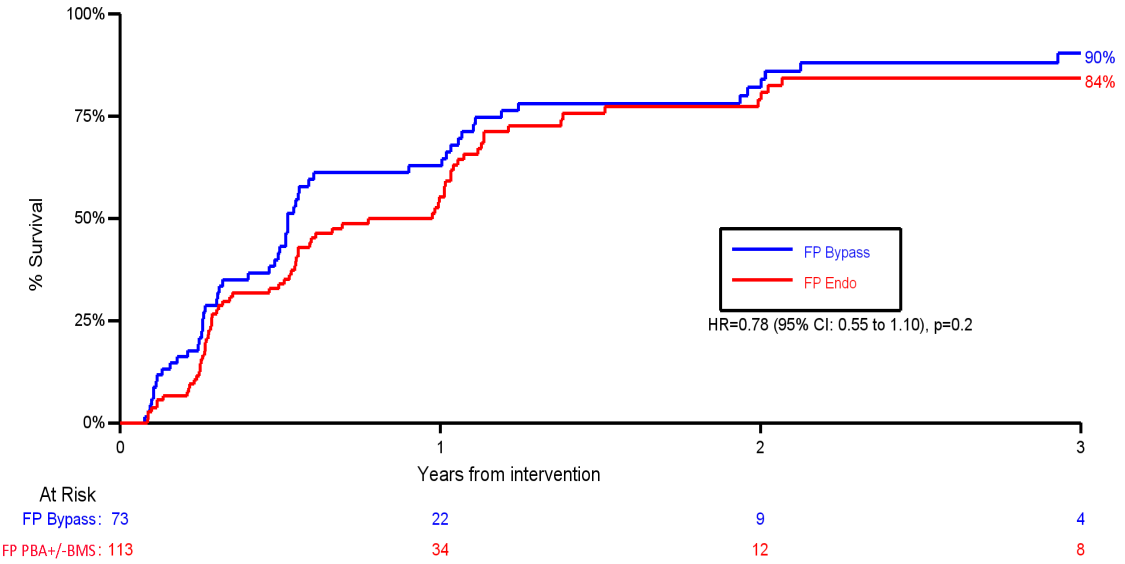


Figure 3.1.5 *Cumulative Kaplan Meier estimate of Wound Healing in patients undergoing (FP) bypass and plain balloon angioplasty +/- bare metal stent (PBA+/-BMS in the BASIL-1 trial*



Long term clinical outcomes VB vs SynB vs PBA+/-BS

There was no significant difference in AFS (67% vs. 51% vs 55%, p = 0.2), OS (72% vs. 64% vs. 63%, p=0.4) and LS (90% vs. 72% vs 85%, p=0.3) between VB, SynB and PBA+/- BMS, although the number of SynB was small. FF-MALE (71% vs 58% vs 56%, p=0.02) was significantly better following VB.

Re-interventions

Overall, 24 (19%) OSB, and 63 (34%) PBA +/- BMS, patients underwent re-intervention, with 38 and 85 re-interventions respectively (**Table 3.1.4)**. There was no difference in the number of inflow procedures performed in each group (7 vs. 8, p=0.2). Patients in the PBA +/- BMS group underwent more secondary bypass procedures (47, 55% vs. 3, 8% p=<0.001) and more repeat angioplasties (21 ,25%, vs 5, 13%, p=0.1). OSB patients underwent more angioplasties for in-graft stenosis (13, 35% vs. 1, 1%, p=<0.001).

Table 3.1.4 *Re-interventions following open surgical bypass and plain balloon angioplasty +/- bare metal stent*

	Re-intervention	OSB (n = 128)	PBA+/-BMS (n = 183)
Number of patients		24 (19%)	63 (34%)
Total re-interventions		38	85
Inflow	Ileo-femoral bypass	2 (5%)	1 (1%)
	Iliac PBA+/- BMS	2 (5%)	4 (5%)
	Axillo-femoral bypass	1 (3%)	0 (0%)
	Aorto-bifemoral bypass	0 (0%)	1 (1%)
	Common femoral endarterectomy	1 (3%)	2 (2%)
	Femoro-femoral crossover	1 (3%)	0 (0%)
FP Revascularisations	OSB	3 (8%)	47 (55%)
	PBA+/-BMS	5 (13%)	21 (25%)
	Graft PBA	13 (34%)	1 (1%)
	Thrombolysis	1 (3%)	1 (1%)
	Embolectomy	3 (8%)	2 (2%)
	Profundoplasty	0 (0%)	2 (2%)
	Graft patch angioplasty	1 (3%)	0 (0%)
Other	Graft explanted for infection	2 (5%)	1 (1%)
	Haemostasis	2 (5%)	0 (0%)
	Chemical Sympathectomy	1 (3%)	2 (2%)

OSB - Open Surgical Bypass
PBA - Plain Balloon Angioplasty
BMS - Bare Metal Stent

DISCUSSION

The main finding of this BASIL-1 FP sub-group analysis is that although major amputation rates and all-cause mortality are similar, primary OSB, especially VB, results in significantly fewer MALE and re-interventions than primary PBA+/-BMS. So, although an endovascular first revascularisation strategy may be a less resource intensive (expensive) and morbid option in the short term, in longer term, this seems unlikely to be the case. Present data add further weight to the argument that, where possible, VB should be offered as the preferred primary revascularisation procedure to most patients presenting with CLTI due to FP disease. This is especially so in standard risk patients (anticipated life expectancy >2 years) who are more likely to enjoy the long-term benefit of VB and less likely to suffer short-term peri-operative morbidity (18, 131, 138-140). Present data support the previously published BASIL-1 IP sub-group outcomes indicating that the durability and quality of revascularisation are better after VB than after PBA(21). In this BASIL-1 FP cohort, unlike in the IP cohort, healing of tissue loss and speed of resolution of rest pain were not significantly different between the two groups. This may be because almost a quarter (23%) of the patients who underwent primary FP PBA +/- BMS required subsequent OSB for persistent or recurrent symptoms of CLTI. Indeed, CLTI patients presenting with the most severe disease in terms of wound, ischaemia and infection(27), seem to be those most likely to enjoy better outcomes following primary VB than primary endovascular intervention. This is especially so given that outcomes following secondary VB after failed primary endovascular intervention are significantly worse than those observed

when VB is used as the primary revascularisation procedure(141, 142). The low rates of best medical therapy (antiplatelet and statin use coupled with smoking cessation) often observed in CLTI studies are worthy of discussion. In the present study, only two-thirds of patients undergoing OSB were on antiplatelet therapy at randomisation (the rate was 10% lower in PBA +/- BMS group) and only about one-third of patients in both groups were on a statin. While better medical therapy is likely to improve CLTI outcomes overall, there is no evidence this would have altered the conclusions of BASIL-1 in terms of the recommendation to offer VB first wherever possible. Thus, in a recent large case series(131), although best medical therapy rates had improved to approximately 80%, the re-intervention rate was 62% for OSB and 52% for PBA at 3 years. These 3 year re-intervention data are worse than those observed in BASIL-1 at 7 years. This is an important observation as endovascular enthusiasts often point to the fact that BASIL-1 is now a relatively old trial (patents randomised between 1999 and 2004) and argue that, if BASIL-1 were to be repeated using modern endovascular techniques and technologies, the trial would show a clear advantage in favour of an endovascular first strategy for most, even perhaps all, patients. While that is possible, there is no evidence to suggest that such an outcome is likely. Indeed, the evidence we have suggests that such an outcome would be unlikely. In particular, with regard to drug coated balloons (DCB) and drug eluting stents (DES), there are no data to show that they improve clinical outcomes in patients with CLTI when compared to PBA +/-BMS(94-101, 103-105). While DES and DES may be associated with better anatomic outcomes, the great majority of the patients entered into the plethora of industry-funded trials had intermittent claudication, underwent treatment of short segment disease, and had short follow up with little or no reporting of clinical outcomes. Even the small minority of patents in these trials who had CLTI were very

largely entered on the basis of rest pain and did not have tissue loss. Other techniques such as laser atherectomy(143) and covered stents(107) have not been widely adopted due to a lack of evidence demonstrating clinical and cost-effectiveness. At the time of writing, there are no published, publicly-funded trials comparing DCB / DES to either PBA or OSB in patients with CLTI. As a result, and given their very considerable additional cost, the UK National Institute for Health and Care Excellence (NICE) have recommended against the use of DCB and DES and are awaiting the outcome of on-going RCTs, specifically BASIL-2(14) and BASIL-3(15) in the UK and BEST-CLI trial(16) in the US before reconsidering the matter. The European Society of Vascular Surgery (ESVS) and European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of patients with peripheral arterial disease(144) specifically state no clinical benefit has been proven for DCB over PBA. Data reported here support the ESC/ESVS guidelines stance that vein bypass surgery for long lesions in patients with CLTI is the first choice method of revascularisation.

CONCLUSION

In conclusion, this BASIL-1 FP sub-group confirms the superiority of VB as the preferred primary FP re-vascularisation procedure for most CLTI patients. However, the results of further publicly funded, pragmatic RCTs, such as BASIL-2, BASIL-3 and BEST-CLI, are required to help answer the many remaining questions regarding the clinical and cost-effectiveness of alternative revascularisation strategies in different subgroups of CLTI patients.

3.2 A COMPARISON OF CLINICAL OUTCOMES BETWEEN PRIMARY BYPASS VERSUS SECONDARY BYPASS AFTER FAILED PLAIN BALLOON ANGIOPLASTY IN THE BYPASS VERSUS ANGIOPLASTY FOR SEVERE ISCHAEMIA OF THE LIMB (BASIL) TRIAL

ABSTRACT

Introduction

Chronic limb threatening ischaemia (CLTI) is a growing global health problem. The UK NIHR HTA-funded BASIL trial is still the only randomised controlled trial to have compared a bypass surgery first with a plain balloon angioplasty (PBA) first strategy for the management of CLTI. In patients who were likely to survive for 2 years and had a suitable vein, primary bypass (PB) was associated with better clinical outcomes. Furthermore, PBA was associated with a high technical and clinical failure rate and many went on to have secondary bypass (SB).

Aim

To compare clinical outcomes following PB and SB in the BASIL trial.

Methods

Demographic, procedural and outcome data were obtained from the BASIL case report forms. Outcomes were amputation free survival (AFS), limb salvage (LS), overall survival (OS), and freedom from revascularisation (FFR). The SB cohort comprises patients whose first trial intervention was PBA and subsequently underwent bypass during follow-up. The PB cohort comprises those patients whose first trial intervention was bypass.

Results

The 190 PB and 49 SB patients were well matched except that the SB patients were more likely to be current smokers. At a median of 7 years, PB was associated with better AFS (PB 60% vs SB 40%; HR=1.58, p=0.04), LS (PB 85% vs SB 73%, p=0.06), and OS (PB 68% vs 51%, p=0.06). FFR was equivalent (PB 53% vs 53%, p=0.3).

Conclusion

In the BASIL trial, clinical outcomes following PB were significantly better than in patients undergoing SB after failed PBA. Prior to treating patients with CLTI with primary PBA, clinicians should consider that if this should fail, the outcome of attempted subsequent bypass is likely to be significantly worse than if PB were attempted.

INTRODUCTION

Although chronic limb threatening ischaemia (CLTI) is a growing global health problem(145, 146), the evidence underpinning the choice of revascularisation strategy remains poor. The UK NIHR HTA-funded Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) trial remains the only randomised controlled trial (RCT) to have compared a 'bypass surgery first' with a 'plain balloon angioplasty (PBA) first' strategy for CLTI due to infra-inguinal disease(147). An intention to treat analysis (ITT) of BASIL outcome data showed that, in patients who were likely to survive for at least 2 years and who had a suitable vein; primary bypass (PB) was led to better clinical outcomes than primary PBA. Furthermore, primary PBA was associated with a high technical and clinical failure rate such that many of the patients went on to have secondary bypass (SB). Despite this 'level 1' evidence in support of surgical bypass as the preferred revascularisation strategy for patients with a suitable vein, enthusiasm for an endovascular-first approach to most, perhaps even all, patients with CLTI continues to grow(148). As a result, vein bypass is increasingly being viewed as a secondary, salvage procedure to be performed when all endovascular revascularisation options have been exhausted(92, 149). There are surprisingly few published reports of outcomes following SB for failed endovascular revascularisation. Furthermore, in the few studies that are available, patient numbers are often small, patients were not randomised, and patients with intermittent claudication and CLTI are often conflate(142, 150, 151). This topic was briefly reported in the analysis by treatment received, only SB within 8 weeks of primary PTA were included and only AFS was reported but no further in depth analyses were performed(152). The aim of

this study, therefore, was to compare clinical outcomes following PB and all SB after failed primary PBA in the BASIL trial.

METHODS

The BASIL trial methodology has been published previously(147). Ethical approval was obtained from the Multi-Centre Research Ethics Committee for Scotland. Briefly, patients with CLTI due to infra-inguinal disease were randomised to either a PB or primary PBA revascularisation strategy between 1999 and 2004. Patients were followed up until death or the censor date of 1 July 2007. This provided all surviving patients with a minimum of 3 years follow-up (median 51, range 0-92, months).

BASIL trial case report forms (CRF) were interrogated to obtain demographic, procedural and outcome data including amputation free survival (AFS), limb salvage (LS), overall survival (OS), and freedom from re-intervention (FFR) defined as any further revascularisation of the index limb. The SB cohort comprises patients whose first trial intervention was PBA and who subsequently underwent SB (with any conduit) at any point during trial follow-up. The PB cohort comprises those patients whose first trial intervention was PB with any conduit. Time to event analyses are presented over a 7-year period using Kaplan-Meier plots. Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the cohorts were compared using t-test, chi-squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

RESULTS

There were 238 attempted primary PBA in the BASIL trial; of these, 69 patients went on to have a secondary intervention, 17 had a tertiary intervention and 7 had a fourth intervention. 25 (36.2%) of the secondary interventions were PBA; of these, 3 (12%) subsequently underwent SB. The remaining 46 SB's were performed after failed primary PBA. In BASIL, 190 patients underwent PB.

The 190 PB and the 49 SB patients were well matched at the time of randomisation in terms of baseline demographics except that the SB patients were more likely to be current smokers (**Table 3.2.1**). Medical management was also similar (**Table 3.2.2**). 49% (24/49) of those who went on to have SB had a technically successful primary PBA. Tissue loss was present in most patients in both groups (ulcer 62% vs 69% p=0.3, gangrene 34% vs 29% p=0.5). The median time interval between primary PBA and SB was 0 months (range 0-20 months). Of those who underwent PB, 9.5% (18/190) underwent secondary PTA, 94.4% (17/18) of these were for vein graft stenosis and 100% survived with their limb at the end of trial follow up.

Table 3.2.1 *Comparison of primary and secondary bypass patients in the BASIL trial*

		Primary Bypass	**Secondary Bypass**	**p-value**
Number of Patients		190	49	
Age (years)	Mean (SD)	72 (9.3)	73 (7.3)	0.4
	Range	39 – 98	58 – 87	
Gender	Male	127 (66%)	28 (57%)	0.2
Limb	Left	105 (55%)	27 (55%)	1.0
	Right	85 (45%)	22 (45%)	
ABPI	Mean (SD)	0.5 (0.18)	0.48 (0.11)	0.5
Smoker	Never	30 (16%)	12 (24%)	**0.05**
	Ex	86 (45%)	13 (27%)	
	Current	74 (39%)	24 (49%)	

Diabetes	No	113 (60%)	23 (47%)	0.2
	IDDM	31 (16%)	12 (24%)	
	NIDDM	46 (24%)	14 (29%)	
Hypercholesterolemia	No	45 (24%)	11 (22%)	0.6
	Yes, untreated	22 (11%)	3 (6%)	
	Yes, treated	66 (35%)	17 (35%)	
	No record of assessment	57 (30%)	18 (37%)	
Hypertension	No	77 (41%)	19 (39%)	0.8
	Yes, untreated	12 (6%)	2 (4%)	
	Yes, treated	101 (53%)	28 (57%)	
Mobility	Independent	91 (48%)	22 (45%)	0.8
	Cane	79 (41%)	22 (45%)	
	Prosthesis	2 (1%)	1 (2%)	
	Wheelchair	13 (7%)	4 (8%)	
	Bed bound	5 (3%)	0 (-)	
Myocardial Infarction	Yes	26 (14%)	8 (16%)	0.6
Angina	No	153 (81%)	44 (90%)	0.2
	Yes, on exercise	31 (16%)	3 (6%)	
	Yes, at rest	6 (3%)	2 (4%)	
TIA	Yes	19 (10%)	1 (2%)	**0.07**
Stroke	Yes	25 (13%)	6 (12%)	0.9
Rest Pain	Yes	170 (89%)	45 (92%)	0.6
Ulcer	Yes	117 (62%)	34 (69%)	0.3
Gangrene	Yes	64 (34%)	14 (29%)	0.5
Creatinine	N	186	45	
	Mean (SD)	116 (79.4)	111 (62.0)	0.7
	Range	50 – 702	40 – 452	

IDDM - Insulin Dependent Diabetes Mellitus
NIDDM - Non-Insulin Dependent Diabetes Mellitus
TIA - Transient Ischaemic Attack
ABPI - Ankle Brachial Pressure Index

Table 3.2.2 *Medical management in patients undergoing primary and secondary bypass in BASIL*

		Primary Bypass	Secondary Bypass	p-value
Number of Patients		190	49	
Antiplatelet	None	52 (27%)	17 (35%)	0.2
	Single	111 (59%)	24 (49%)	
	Double	2 (1%)	1 (2%)	
	Antiplatelet + Other	15 (8%)	1 (2%)	
	Other	10 (5%)	6 (12%)	
Antihypertensive	None	81 (43%)	18 (37%)	0.3
	One	53 (28%)	19 (39%)	
	Two	40 (21%)	6 (12%)	
	Two or more	16 (8%)	6 (12%)	
Statin	None	123 (65%)	31 (63%)	0.8
	Yes	67 (35%)	18 (37%)	
Diabetes Treatment	None	131 (69%)	25 (51%)	0.1

At a median of 7 years, PB was associated with significantly better AFS (PB 60% vs SB 40%; HR=1.58, 95% CI: 1.03-2.44, p=0.04). Although LS and OS did not reach statistical significance there was a trend to better outcomes in the PB group (LS; PB 85% vs SB 73%; HR=1.86, 95% CI: 0.97-3.58, p=0.06, and OS; PB 68% vs 51%; HR=1.57, 95% CI:0.97-2.54, p=0.06). FFR was the same in both groups (PB 53% vs 53%; HR=1.43, CI:0.74-2.74, p=0.3) except that, of course, by definition, those patients undergoing SB were all undergoing a re-intervention (**Figures 3.2.1-4**).

Figure 3.2.1 *Comparison of amputation free survival in patients undergoing primary and secondary bypass in the BASIL trial*

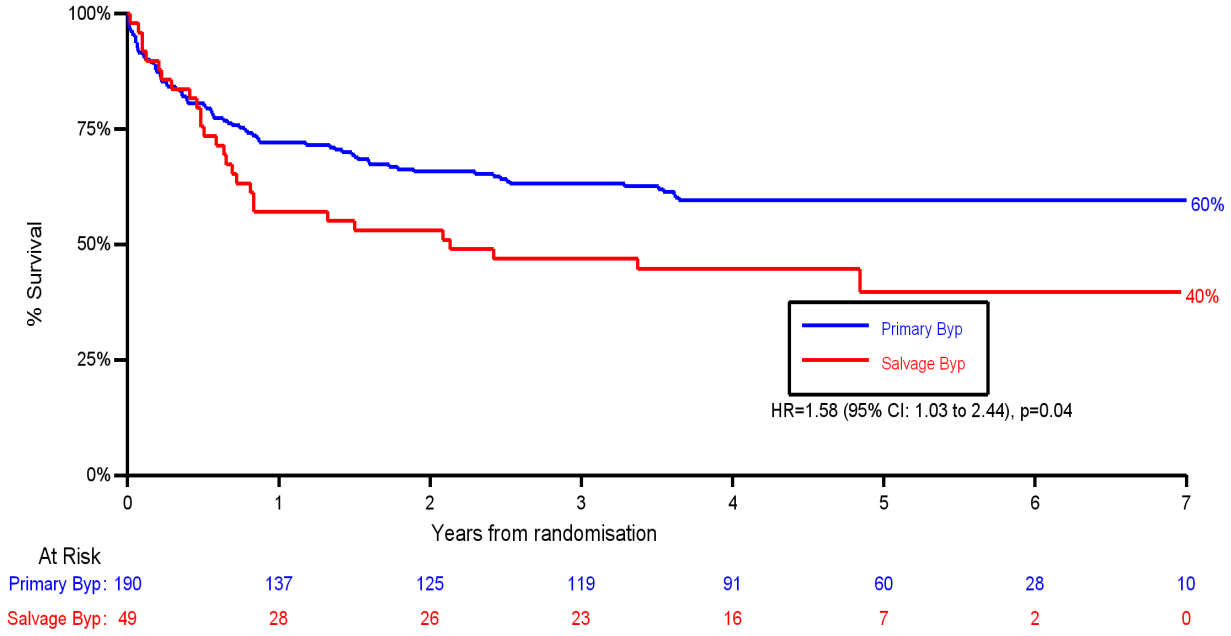


Figure 3.2.2 *Comparison of limb salvage in patients undergoing primary and secondary bypass in the BASIL trial*

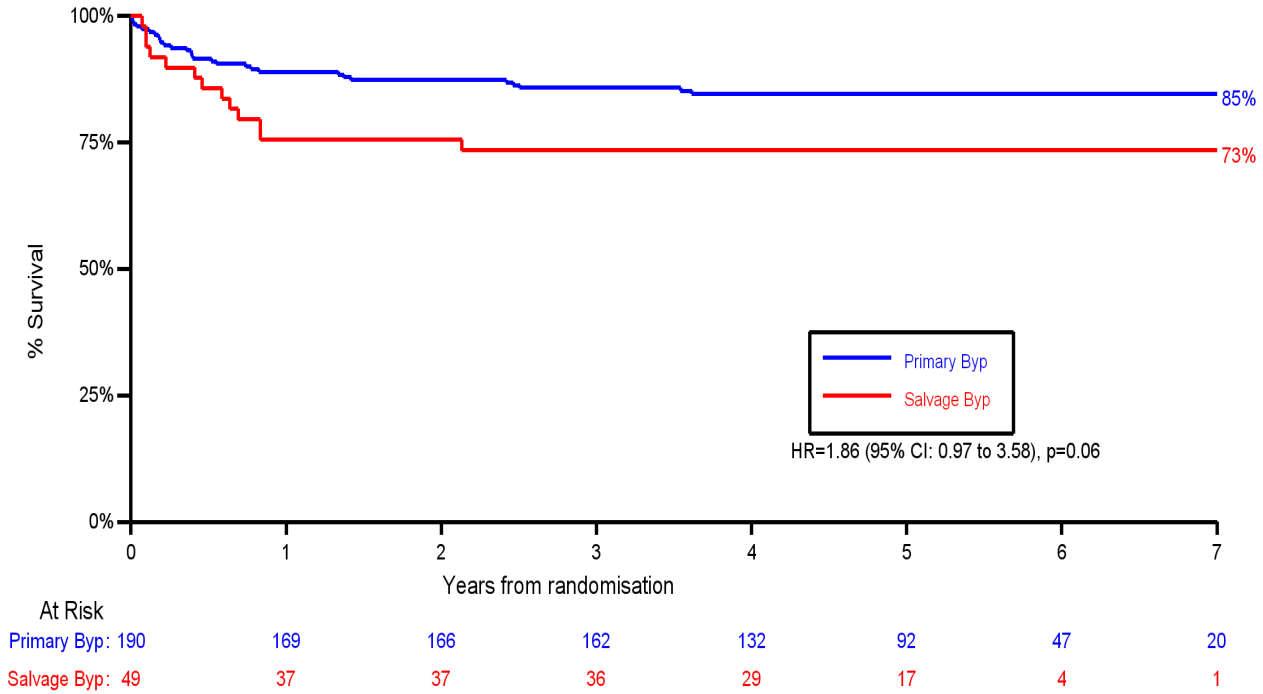


Figure 3.2.3 *Comparison of overall survival in patients undergoing primary and secondary bypass in the BASIL trial*

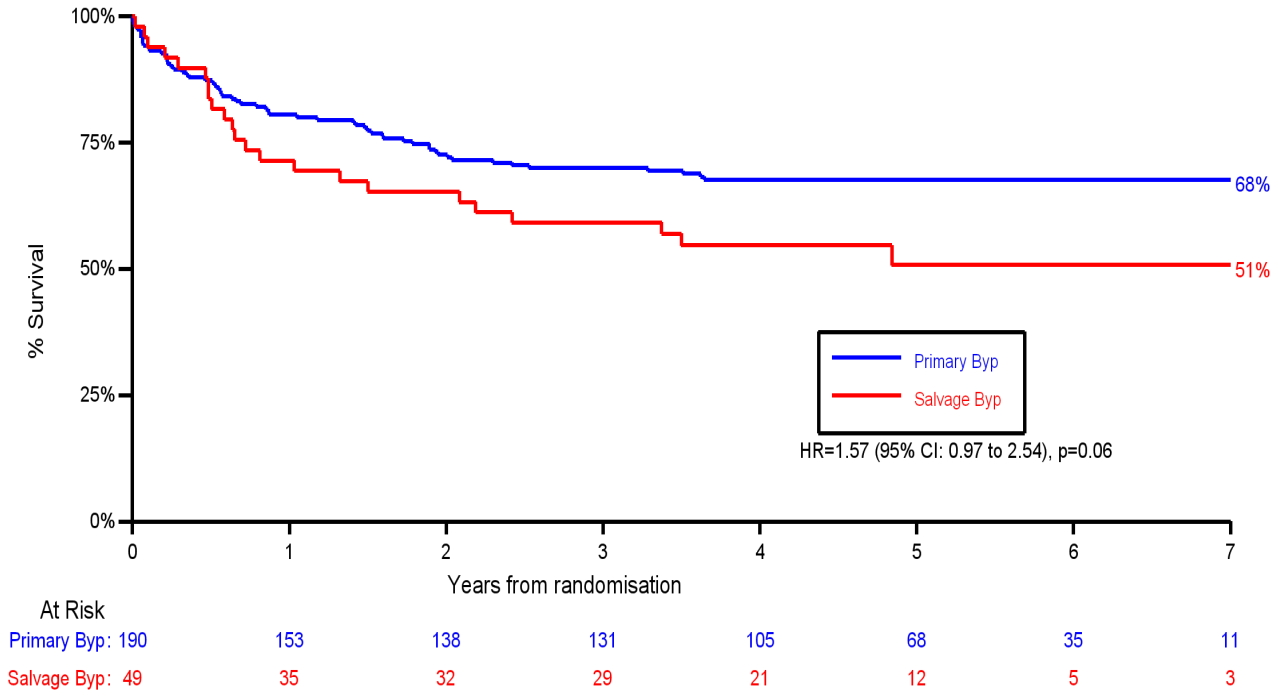
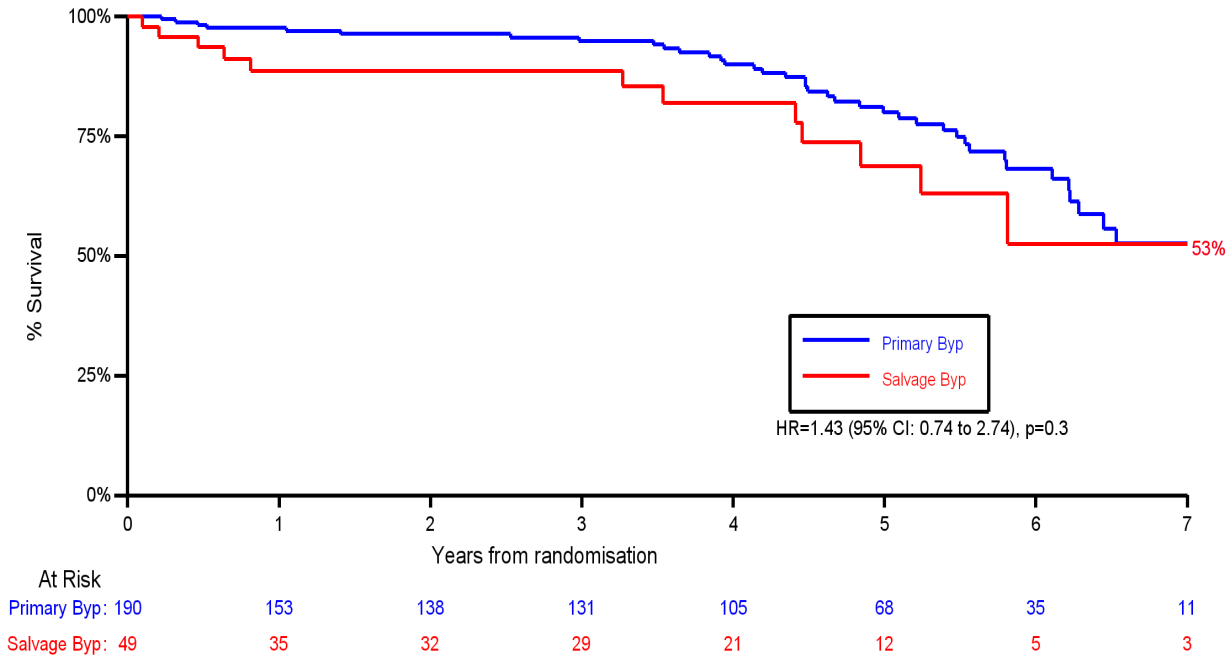


Figure 3.2.4 *Comparison of freedom from re-intervention in patients undergoing primary and secondary bypass in the BASIL trial*



Procedural data were available for all patients who underwent SB (**Table 3.2.3**). All SB were deemed technically successful at the end of the procedure. Four (8%) SB were prosthetic compared with 22% (41/190) PB (p=0.03). Absolute amputation rate to end of follow up was 15.3% vs 26.5% (p=0.06). The distal anastomosis was not statistically different between PB and SB with 68% (130/190) vs 64% (31/49) being to the popliteal artery (p=0.4). There was no significant difference between PB and SB in terms of 30-day morbidity and mortality (**Table 3.2.4**).

Table 3.2.3 *Frequencies of proximal and distal anastomosis location for primary and secondary bypass*

		Primary Bypass	Secondary Bypass	p-value
Number of Patients		190	49	
Distal Anastomosis	Not Known	2 (1%)	0 (-)	0.4
	AKPA	63 (33%)	10 (20%)	
	BKPA	67 (35%)	21 (44%)	
	PTA	17 (9%)	2 (4%)	
	ATA	20 (11%)	9 (18%)	
	PA	17 (9%)	6 (12%)	
	DP	2 (1%)	0 (-)	
	TPS	1 (0.5%)	1 (2%)	
	DPP	1 (0.5%)	0 (-)	
Conduit	Vein	149 (78%)	45 (92%)	0.03
	Synthetic	41 (22%)	4 (8%)	

AKPA - Above Knee Popliteal Artery
BKPA - Below Knee Popliteal Artery
PTA - Posterior Tibial Artery
ATA - Anterior Tibial Artery
PA - Peroneal Artery
DP - Dorsalis Pedis
TPS - Tibial Peroneal Stem
DPP - Dual Popliteal and Pedal

Table 3.2.4 *Mortality and morbidity (30 days) in patients undergoing primary and secondary bypass in BASIL*

	Primary Bypass	Secondary Bypass	p-value
Number of Patients	190	49	
Angina	2 (1%)	0 (-)	0.5
MI	8 (4)	2 (4)	1.0
TIA	0 (-)	0 (-)	-
CVA	1 (0.5%)	1 (2%)	0.3
Haematoma (no surgery)	8 (4%)	1 (2%)	0.5
Haematoma (surgery)	3 (2%)	0 (-)	0.4
LRTI	6 (3%)	1 (2%)	0.7
UTI	9 (5%)	1 (2%)	0.4
False Aneurysm (no surgery)	1 (0.5%)	0 (-)	0.6
False Aneurysm (surgery)	0 (-)	0 (-)	-
30 Day Mortality	11 (6%)	4 (8%)	0.5
30 Morbidity & Mortality	83 (44%)	19 (39%)	0.5
MACE	17 (9%)	6 (12%)	0.5

MI – Myocardial Infarction
TIA - Transient Ischaemic Attack
CVA - Cerebro-Vascular Accident
LRTI - Lower Respiratory Tract Infection
UTI - Urinary Tract Infection
MACE - Major Adverse Cardiac Event

Table 3.2.5 *A comparison of Bollinger scores between primary and secondary bypass.*

SEGMENT	STATS	PB	SB	P-VALUE
Profunda	MEAN (SD)	2.4 (3.4)	2.5 (3.6)	0.828
Proximal SFA	MEAN (SD)	6.7 (5.6)	5.8 (5.3)	0.3
Distal SFA	MEAN (SD)	9.2 (5.4)	10.4 (5.0)	0.2
Proximal POP	MEAN (SD)	6.6 (5.7)	7.3 (6.3)	0.5
Distal POP	MEAN (SD)	3.7 (5.1)	3.7 (5.1)	1.0
TPT	MEAN (SD)	4.1 (5.8)	2.8 (5.0)	0.2
Proximal PT	MEAN (SD)	8.5 (7.0)	8.7 (7.0)	0.9
Distal PT	MEAN (SD)	9.7 (6.5)	9.2 (6.9)	0.7
Proximal AT	MEAN (SD)	6.9 (6.5)	8.5 (7.0)	0.2
Distal AT	MEAN (SD)	7.3 (6.9)	8.7 (7.0)	0.3
Proximal PERO	MEAN (SD)	4.8 (5.8)	4.2 (5.9)	0.6
Distal PERO	MEAN (SD)	5.5 (6.5)	2.2 (5.0)	**0.005**
Total FP score	MEAN (SD)	25.7 (9.9)	26.3 (9.0)	0.7
Total IP score	MEAN (SD)	45.3 (24.8)	46.3 (26.6)	0.8
Total score	MEAN (SD)	71.1 (26.4)	72.7 (26.6)	0.8

SFA – Superficial Femoral Artery
POP - Popliteal Artery
TPT - Tibio-Peroneal Trunk
PT – Posterior Tibial Artery
AT - Anterior Tibial Artery
PERO - Peroneal Artery
SD - Standard Deviation

DISCUSSION

In the BASIL trial, 190 patients underwent PB and, of the 238 patients who underwent an attempt at primary PBA, 49 (21%) went on to require a SB at some point during the trial follow-up. The key finding of the present study is that PB was associated with statistically significant better AFS and a strong trend ($p = 0.06$) towards better LS and OS. We accept the SB group are a group of failures which suggests they are different to the PB group, the challenge for this analysis is to identify why? We also accept the BASIL trial was not powered to investigate this relationship, nevertheless it is an important relationship that is poorly understood. The two cohorts were well matched in terms of baseline demographics and medical therapy at randomization, PB patients were more likely to be current smokers and have a history of TIA, however we note this group was observed to have better clinical outcomes. This suggests the observed differences are not related to the patient's medical characteristics. Anatomical burden of disease is certainly influential in type of revascularization required and outcome of said intervention. Bollinger analysis of these groups suggests there is no difference in burden or distribution of disease between these groups.

The appropriateness of the observed trend in recent years towards an endovascular first strategy for most, perhaps even all, CLTI is now being challenged(138, 153, 154). However, although several groups have reported outcomes following PB and primary endovascular revascularisation, few have analysed the effect of failed endovascular intervention on the success of SB. But, these reports, taken with the data from the BASIL trial presented here, indicate that primary endovascular intervention is not the "free shot" that it has so often been claimed to be.

Although BASIL trial data are often said to be outdated and so no longer relevant to current practice, in reality, there is no evidence that that is the case(142). For example, Darling and colleagues recently studied 2869 patients undergoing lower limb revascularisation for CLTI and concluded that PB resulted in better outcomes in wound healing, FFR and OS; and that patients undergoing SB had higher rates of further intervention(155). In another study, Jones and co-workers analysed 1154 CLTI patients undergoing SB and concluded these patients had worse MALE, FFR, OS and AFS(131).

Interestingly, although more BASIL patients in the PB group underwent synthetic bypass (PB 22% SB 8%), overall, the clinical results of PB were far superior to those observed after SB. In the UK, synthetic grafts are almost always reserved for those patients with no usable leg or arm vein(132, 156, 157) [17-19]. As such, it could be argued patients undergoing prosthetic bypass should have been removed from this analysis. However, we decided to include them as a proportion CLTI patients requiring bypass will not have useable vein. Approximately a third of the patients in each group underwent infra-popliteal bypass and so we can discount this as a cause of the differences observed between PB and SB.

Going forward, it will be important to determine if drug coated balloons and drug eluting stents will increase the clinical success of primary endovascular intervention for CLTI. The on-going UK NIHR HTA funded BASIL 2 and 3 trials(14, 15), and US NIH funded BEST CLI trial(16), will together recruit more than 3,500 CLTI patients undergoing PB and primary endovascular intervention and will address this and many other important question so informing evidence-based revascularisation (EBR).

CONCLUSION

In the BASIL trial, clinical outcomes following PB were significantly better than in patients undergoing SB after failed PBA. Prior to treating patients with CLTI with primary PBA, clinicians should consider that if this should fail, the outcome of attempted subsequent bypass is likely to be significantly worse than if PB were attempted.

3.3 COMPARISON OF CLINICAL OUTCOMES FOLLOWING FEMORO-POPLITEAL PLAIN BALLOON ANGIOPLASTY WITH OR WITHOUT BARE METAL STENTING FOR CHRONIC LIMB THREATENING ISCHAEMIA IN THE BASIL TRIAL AND IN A CONTEMPORARY SERIES FROM A UK ACADEMIC VASCULAR UNIT

ABSTRACT

Background

Advances in endovascular devices have driven a non-evidence-based, world-wide trend towards an increasingly endovascular first revascularisation strategy for chronic limb threatening (CLTI). There is growing concern that this may be inappropriate and can potentially result in net patient harm. The aim of this study, therefore, is to compare clinical outcomes following femoro-popliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS) in a contemporary series (CS) (treated 2009-2014) from a UK academic vascular unit with those observed following FP-BBA +/- BMS in the UK NIHR HTA-funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1, B1) trial (treated 1999-2004).

Methods

Baseline and clinical outcome data (amputation free survival, AFS; overall survival, OS; limb salvage, LS; freedom from re-intervention, FF-R; freedom from major adverse limb events, FF-MALE) were obtained from prospectively gathered hospital data and B1 trial case record forms.

Results

There were 237 CS and 218 B1 patients. CS patients were older (77 vs 73 years, p=0.0002). B1 patients were more likely to be current smokers, less likely to be on best medical therapy, and had more extensive endovascular interventions. CS patients spent more time in hospital (31 vs 27 days, p=0.8), and had more hospital admissions (4 vs 2, p<0.0001), before they reached their primary endpoint (AFS). Immediate technical success was non-significantly higher in the CS (87% vs 83%, p=0.2). BMS were used in 20 (8%) CS and 2 (1%) B1 patients (p=0.0002). Out to 7 years, AFS (HR = 0.64, 95%CI: 0.49 to 0.82, p = 0.0005) and OS (HR = 0.58, 95% CI: 0.44 to 0.76, p = 0.0001) were significantly worse in the CS cohort. There was no significant difference in LS, FF-R or FF-MALE.

Conclusions

This study suggests that patients being treated with an indiscriminate endovascular first revascularisation strategy for CLTI experience worse long-term clinical outcomes compared to those treated within the B1 trial.

Chronic limb threatening ischaemia (CLTI) is estimated to affect 500-1000 per million population in developed countries and, although reliable epidemiological data are limited, it is widely accepted that the incidence is increasing rapidly in the so-called emerging economies and developing world(6). The prognosis for most people with CLTI remains extremely poor in terms of limb loss and premature mortality(158). Despite this, the evidence base underpinning the treatments of these patients, especially mode of revascularisation is poor. As a result, there has been an increased trend to primary endovascular revascularisation in patients with CLTI(92) despite the UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) funded Bypass versus Angioplasty for Severe Ischaemia of the Leg trial (BASIL-1, B1) concluding that acceptable risk patients being treated with bypass surgery had superior clinical outcomes(20). This message has been reflected in more recent non-randomised data(131, 138, 159-161), however the authors accept there are other conflicting case series contradicting this conclusion, combined analysis of the limited available data indicates better technical and long-term clinical outcomes for bypass surgery(162). Our unit for example employs an endovascular first strategy to revascularising patients with CLTI, like many others(163), reserving bypass surgery for patients who either are not suitable for or fail endovascular intervention. With this, non-evidence based, change in practise it is important to investigate whether a non-selective endovascular revascularisation strategy is providing superior clinical results to that observed historically (B1). The aim of this study, therefore, was to compare outcomes following femoro-popliteal (FP) PBA +/- BMS in a contemporary series (CS) of CLTI patients treated between 2009 and 2014 in a single UK academic vascular

unit with those observed in patients randomised in B1 to FP-PBA +/- BMS between1999 and 2004.

METHODS

Baseline and clinical outcome data (amputation free survival, AFS; overall survival, OS; limb salvage, LS; freedom from re-intervention, FF-R; and freedom from major adverse limb events, FF-MALE) in CS and B1 patients undergoing FP-PBA +/- BMS as part of their primary endovascular revascularisation for CLTI were obtained from prospectively gathered hospital data, electronic databases, and B1 case record forms. Patients were included if they were suffering with CLTI (ulceration, gangrene, ischaemic rest pain) and met the anatomical inclusion criteria for entry into the BASIL–3 trial; namely, they had predominantly FP disease +/- infra-popliteal (IP) disease. B1 patients underwent their intervention between 12/08/1999 and 23/06/2004, and CS patients about ten years later between 01/01/2009 and 31/12/2014. B1 data were censored on 01/07/2007 and CS data on 31/05/2017.

FF-R was defined as absence of attempted revascularisation of the index limb or interventions relating to complications of the primary procedure. Minor amputations (distal to tarsal bones) were not considered a re-intervention as they were considered a likely a consequence of the severity of the presenting clinical condition rather than type of revascularisation. MALE were defined as any attempt at revascularisation or a major amputation (above ankle) of the index limb during the trial period. Technical success was defined by the interventionist as successfully deployed treatment with satisfactory angiographic appearance at the end of the procedure.

CLTI is the more up to date term which is now used to encompass what was previously described as Critical Limb Ischaemia and Severe Limb Ischaemia before that. In BASIL the patients included were defined as suffering from Severe Limb Ischaemia (SLI), in practise these patients were suffering with either gangrene, ischaemic ulceration and/or rest pain therefore are equivalent to what would be included by the term CLTI.

As part of BASIL-1 angiograms were collected and Bollinger(164) scored to quantify the burden of disease treated within the trial. Not all patients had angiograms provided, and of the 218 patients included in this work, 196 had Bollinger scores for analysis. Patients in the CS were also Bollinger scored to provide a comparison of disease burden. More recently the Global Vascular Guidelines(26) have introduced the Global Anatomic Staging System (GLASS) score to help guide decisions on which patients are likely to benefit from endovascular revascularisation. Angiograms from the BASIL trial and the CS were reviewed and GLASS scored to further add a description of likely success of endovascular treatment for each cohort.

The primary endpoint of this study was AFS. Secondary endpoints were OS, LS, FF-R, MALE and technical success. Out to 7 years, Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the cohorts were compared using t-test, χ^2-squared, Fisher's Exact test and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

RESULTS

There were 237 and 218 patients in the CS and B1 cohorts respectively. CS patents were older (77 vs 73 years, p=0.0002) and more patients suffered with rest pain (with or without tissue loss) in the BASIL group but otherwise the cohorts were well-matched in terms of baseline co-morbidities and vascular risk factors (**Table 3.3.1**). B1 patients were more likely to be current smokers and less likely to be on best medical therapy.

They also had a significantly higher burden of disease (FP Bollinger total 44.8 vs 39.4, p=0.031) and more likely to have more than three arterial segments treated (12% vs 25%, p=0.004 (**Table 3.3.2**).

Table 3.3.1 *Baseline data in the CS and B1 cohorts*

		CS (n = 237)	B1 (n = 218)	p-value
Age (years)	Mean (SD)	77 (11.1)	73 (8.6)	0.0002
	Range	38 – 99	46 – 95	
Gender	Male	130 (55%)	118 (54%)	0.9
Clinical presentation	Rest pain only	75 (32%)	79 (36%)	<0.0001
	Tissue loss only	131 (55%)	15 (7%)	
	Both	31 (13%)	123 (56%)	
	neither	0 (0%)	1(1%)	
Smoking status	Never	24 (10%)	0 (-)	<0.0001
	Ex	26 (11%)	47 (21%)	
	Current	36 (15%)	69 (32%)	
	Unknown	151 (64%)	102 (47%)	
Creatinine	Mean (SD)	99 (64.5)	109 (56.5)	0.1
	Range	0 – 642	28 – 633	
	Unknown	0	12	
DM	No	152 (64%)	127 (58%)	0.2
	Yes	85 (36%)	91 (42%)	
CHF	No	214 (90%)	209 (96%)	0.02
	Yes	23 (10%)	9 (4%)	
HTN	No	83 (35%)	82 (38%)	0.6
	Yes	154 (65%)	136 (62%)	
CAD	No	180 (76%)	158 (72%)	0.4
	Yes	57 (24%)	60 (28%)	

COPD	No	210 (89%)	203 (93%)	0.1
	Yes	27 (11%)	15 (7%)	
Statin	No	75 (32%)	140 (64%)	<0.0001
	Yes	147 (62%)	78 (36%)	
	Unknown	15 (6%)	0 (-)	
Other lipid lowering drug	No	211 (89%)	216 (99%)	<0.0001
	Yes	11 (5%)	2 (1%)	
	Unknown	15 (6%)	0 (-)	
Antiplatelet	No	69 (29%)	97 (45%)	<0.0001
	Yes	154 (65%)	121 (55%)	
	Unknown	14 (6%)	0 (-)	
Anticoagulant	No	191 (81%)	204 (94%)	<0.0001
	Yes	31 (13%)	14 (6%)	
	Unknown	15 (6%)	0 (-)	
ACE inhibitor	No	122 (52%)	152 (70%)	<0.0001
	Yes	100 (42%)	66 (30%)	
	Unknown	15 (6%)	0 (-)	
Beta Blocker	No	167 (71%)	193 (89%)	<0.0001
	Yes	55 (23%)	25 (11%)	
	Unknown	15 (6%)	0 (-)	

DM – Diabetes Mellitus
CHF - Congestive Heart Failure
HTN - Hypertension
CAD - Coronary Artery Disease
COPD - Chronic Obstructive Pulmonary Disease
ACE - Angiotensin-converting-enzyme
SD - Standard Deviation

Table 3.3.2 *Summary of Bollinger and GLASS scores by cohort*

Arterial Segment	Units	CS Endo	B1 Endo	P Value
Profunda	Mean (SD)	0.76 (2.6)	2.43 (3.8)	<0.000
Proximal SFA	Mean (SD)	4.3 (4.8)	6.6 (5.4)	<0.000
Distal SFA	Mean (SD)	6.6 (5.3)	9.9 (5.0)	<0.000
Proximal Popliteal	Mean (SD)	6.8 (5.4)	7.1 (5.7)	0.520
Distal Popliteal	Mean (SD)	3.9 (5.2)	3.2 (4.5)	0.145
TPT	Mean (SD)	3.5 (5.5)	3.6 (4.9)	0.787
AT Proximal	Mean (SD)	5.9 (6.8)	6.8 (6.0)	0.144
AT Distal	Mean (SD)	5.7 (7.1)	7.3 (6.7)	0.019
PT Proximal	Mean (SD)	7.8 (8.1)	8.8 (6.2)	0.131
PT Distal	Mean (SD)	8.0 (8.3)	9.4 (6.4)	0.037
Peroneal Proximal	Mean (SD)	4.5 (6.2)	4.9 (5.3)	0.425
Peroneal Distal	Mean (SD)	4.2 (6.5)	4.4 (5.6)	0.682
Total Score	Mean (SD)	61.8 (32.0)	73.8 (27)	0.000
Femoro-popliteal total Score	Mean (SD)	39.4 (28.2)	44.8 (23.4)	0.031
Infra-popliteal total score	Mean (SD)	22.4 (12.3)	29.2 (11.1)	<0.000
FP GLASS Grade	Mean (SD)	237	196	
0	N (%)	0	1	
1	N (%)	13	21	
2	N (%)	29	35	
3	N (%)	62	43	
4	N (%)	133	96	0.060
IP GLASS				
0	N (%)	166	137	
1	N (%)	15	22	
2	N (%)	23	18	
3	N (%)	11	5	
4	N (%)	22	11	0.185
GLASS Score				
1	N (%)	30	38	
2	N (%)	64	54	
3	N (%)	143	103	0.137

SFA - Superficial Femoral Artery

TPT - Tibio-Peroneal Trunk

AT - Anterior Tibial Artery

PT - Posterior Tibial Artery

GLASS - Global Anatomic Staging System

CS patients were more likely to suffer from 30-day myocardial infarction (5% vs 1%, p=0.01) and cerebrovascular event (6% vs 2%, p=0.03). However, 30-day mortality was not significantly different between the two groups (4% vs 3%, p=0.5). CS patients spent less time in hospital during their index admission (3 vs 8 days, p<0.0001) and over the first 12 months (12 vs 19 days, p=0.002). However, CS patients spent more time in hospital (31 vs 27 days, p=0.8), and had more hospital admissions (4 vs 2, p<0.0001) before they reached the primary endpoint (AFS, death from any cause or major amputation, whichever occurred first). Immediate technical success, as adjudicated by the interventional radiologist performing the procedure, was non-significantly higher in the CS cohort (87% vs 83%, p=0.2). BMS were used in 20 (8%) CS and 2 (1%) B1 patients (p=0.0002). Out to 7 years, AFS (HR = 0.64, 95% CI: 0.49 to 0.82, p = 0.0005) (**Figure 3.3.1**) and OS (HR = 0.58, 95% CI: 0.44 to 0.76, p = 0.0001) (**Figure 3.3.2**) were highly significantly worse in the CS cohort.

Figure 3.3.1 *Amputation Free Survival (AFS) in a contemporary series (CS) and BASIL (B1) patients undergoing femoro-popliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS)*

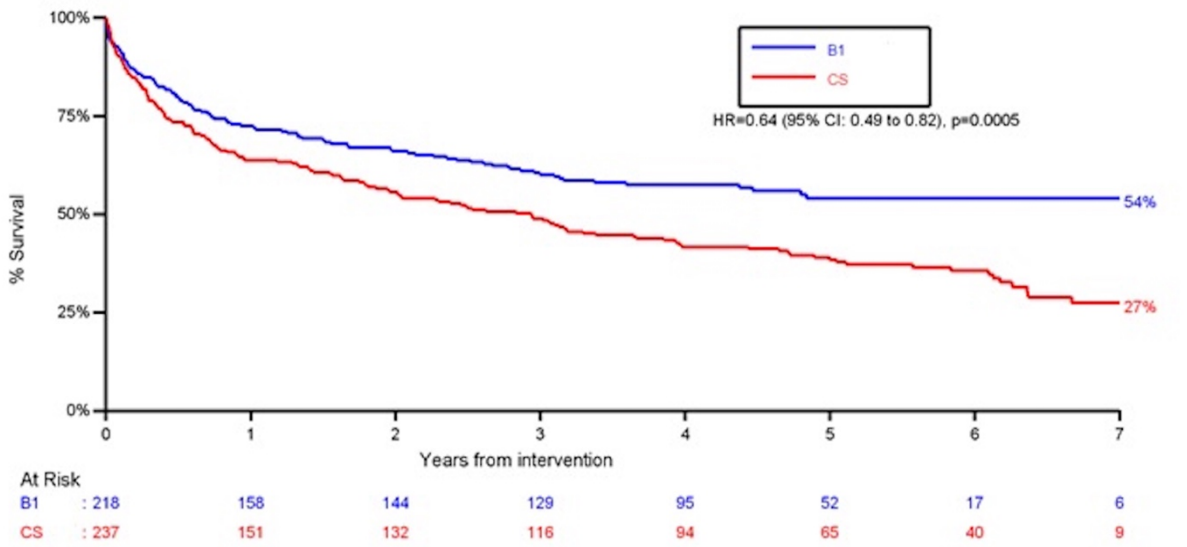
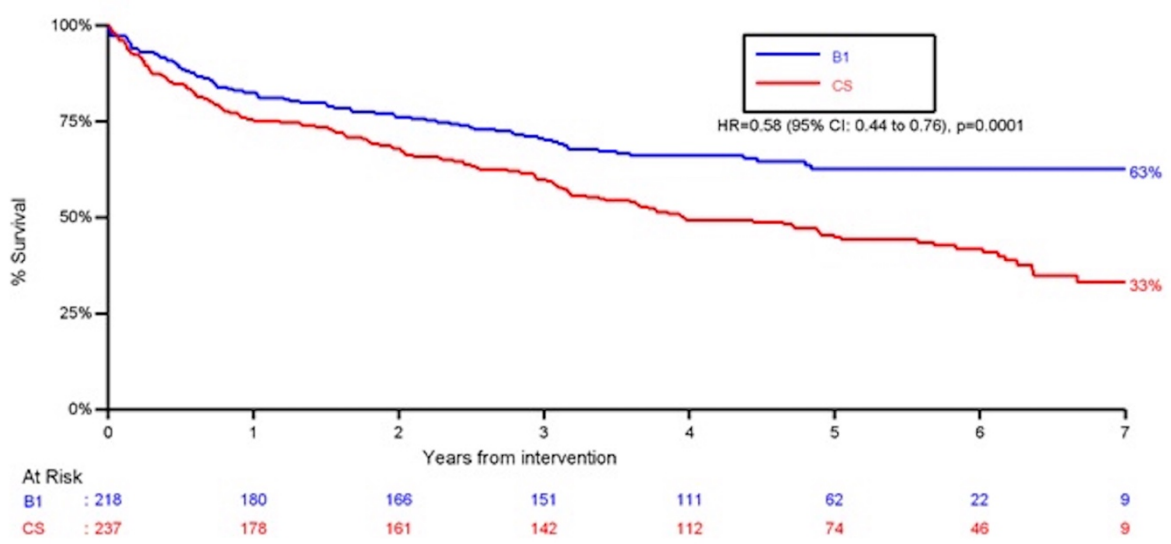


Figure 3.3.2 *Overall Survival (OS) in a contemporary series (CS) and BASIL (B1) patients undergoing femoro-popliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS)*



There was no significant difference in LS (HR=0.75, 95% CI: 0.48 to 1.18, p=0.2) (**Figure 3.3.3**), FF-R (HR=1.19, 95% CI: 0.86 to 1.66, p=0.3) (**Figure 3.3.4**) or FF-MALE (HR=1.02, 95% CI: 0.76 – 1.37, p=0.9) (**Figure 3.3.5**).

Figure 3.3.3 *Limb Salvage (LS) in a contemporary series (CS) and BASIL (B1) patients undergoing femoro-popliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS)*

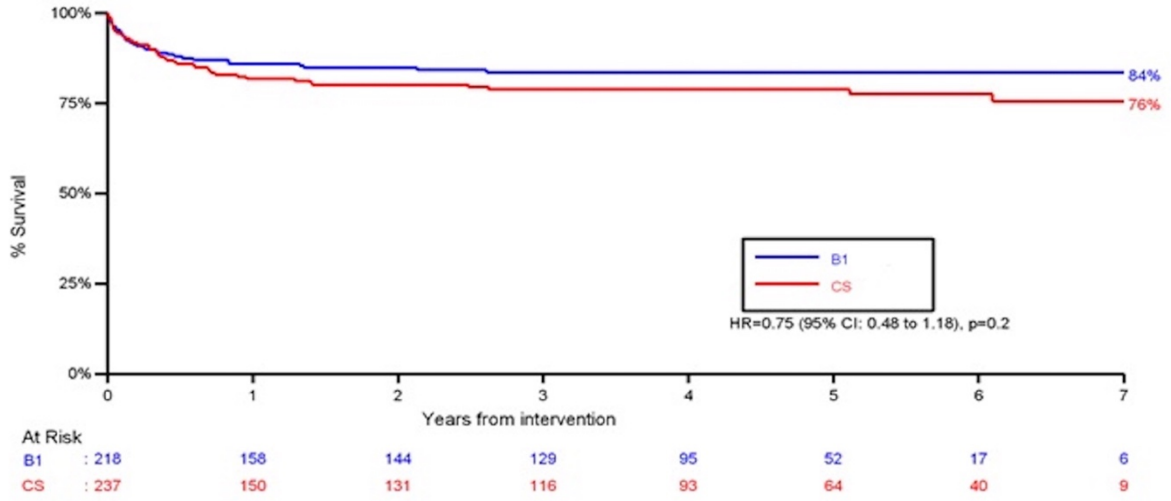


Figure 3.3.4 *Freedom from re-intervention in a contemporary series (CS) and BASIL (B1) patients undergoing femoro-popliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS)*

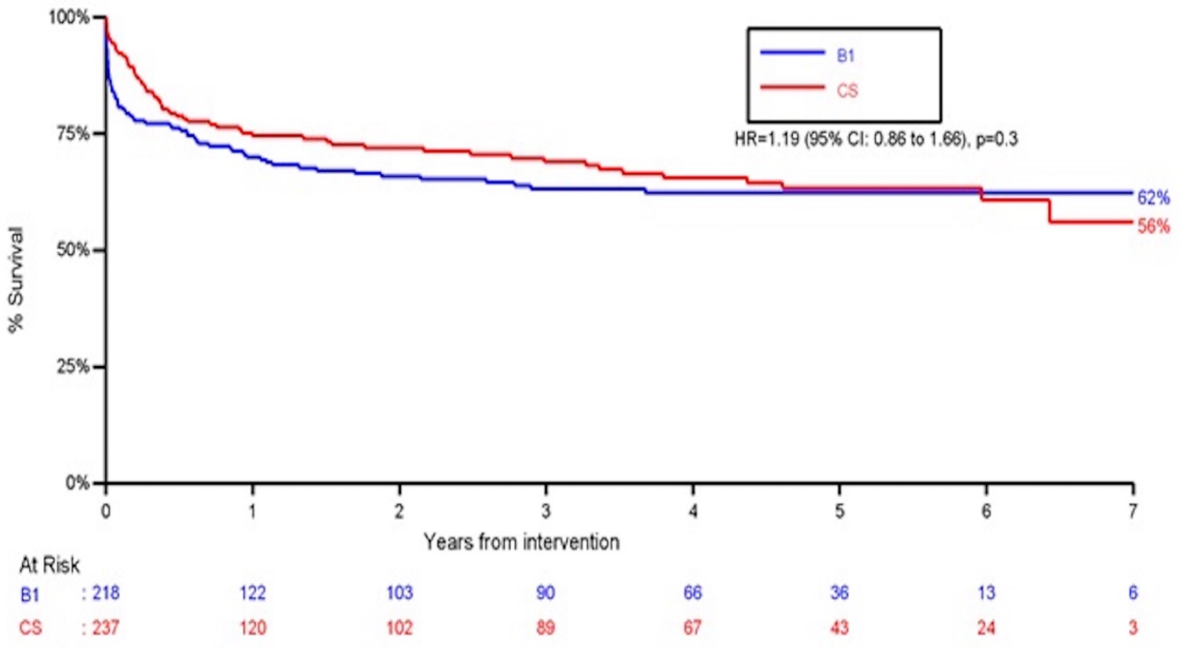
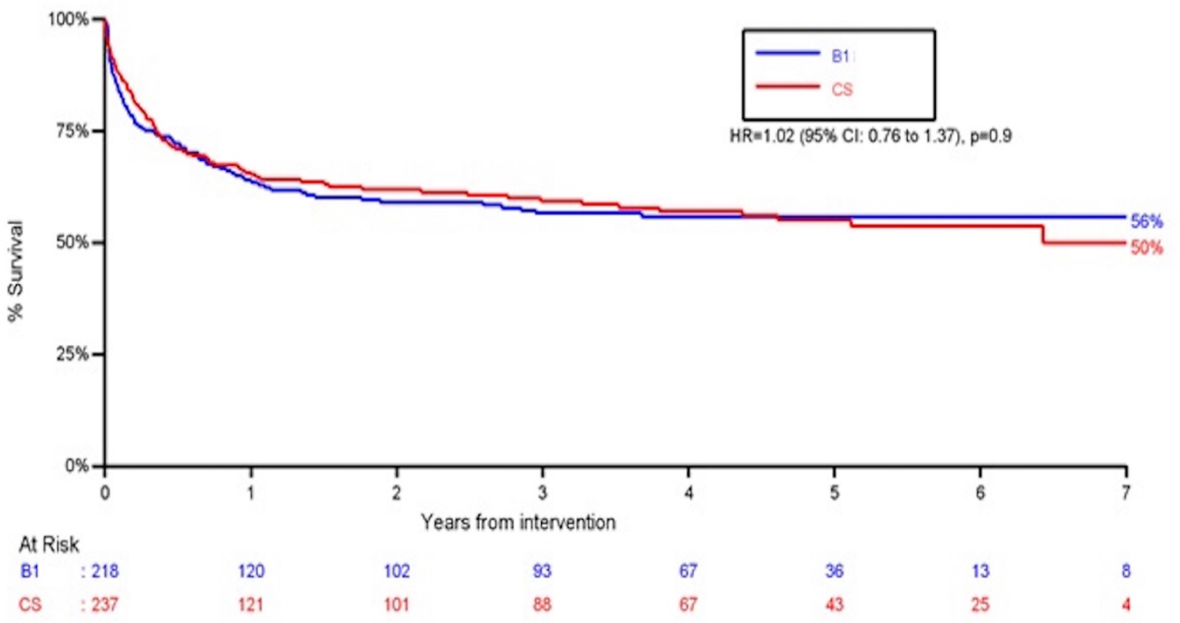


Figure 3.3.5 *Freedom from Major Adverse Limb Events (FF-MALE) in a contemporary series (CS) and BASIL (B1) patients undergoing femoro-popliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS)*



Although there was no difference between re-intervention rates between the two cohorts, B1 patients were more likely to undergo bypass surgery, as opposed to a further endovascular intervention, as their second revascularisation procedure (69% vs 18%, p=<0.001).

DISCUSSION

The main finding from the present study is that, despite advances in endovascular devices (balloons, catheters and wires) and techniques, and claims that this has resulted in better and more durable anatomic outcomes, in our UK academic vascular unit, outcomes after FP-PBA +/- BMS are no better now (2009-2014) than those observed ten years earlier in the B1 trial (1999-2004). Indeed, AFS and OS are now very significantly worse.

While some may argue that this is because patients are now more co-morbid with more extensive disease, this is not borne out by the present data. Thus, although CS patients were older, the two cohorts were well matched in terms of baseline co-morbidities and vascular risk factors. Furthermore, B1 patients were more likely to be current smokers and less likely to be on best medical therapy (BMT). Interestingly, however, only two-thirds of CS patients were on BMT, indicating a large proportion of patients with CLTI are still not receiving adequate medical therapy.

Although B1 patients had more extensive endovascular interventions and had a significantly higher burden of disease, there was no significant difference in immediate technical success rates(165, 166). Significantly more CS patients had BMS which may explain the small difference observed(167, 168). However, even in the CS, BMS

were infrequently used and then mainly to improve sub-optimal PBA rather than as a primary treatment option(169-171). Readers may think that the stent rate observed here, in patients undergoing complex endovascular revascularisation, is very low and does not reflect global practise. In the UK there is a feeling that the 'leave nothing behind' approach is the most desirable in these patients, as stent occlusion often behaves in the same manner as prosthetic graft occlusion with significant consequences to the affected limb.

We also observed a markedly different approach to secondary interventions. In B1, most patients underwent bypass surgery after failed primary endovascular intervention, whereas in the CS most patients underwent a further endovascular procedure. Despite this very different approach, it did not result in significantly different limb salvage rates. There was however a trend towards improved overall survival after three years in favour of the B1 patients. This did not reach statistical significance and may be a result of the CS patients being significantly older at first treatment.

It is surprising, and obviously disappointing, to find ourselves reporting that the results of PBA+/-BMS in our unit during the period 2009-2014 were very significantly worse than those reported ten years earlier (1999-2004) in the B1 trial. As discussed above, we cannot plausibly argue this was because the CS overall were more co-morbid with worse disease. All of the procedures in the CS were performed by very experienced interventional radiologists, the immediate technical success rate was good, the immediate complication rate (morbidity and mortality) was low, and the hospital stay was short. Indicating the long-term results observed in the CS are not due to sub-optimal technical performance of the index procedure. Perhaps the most plausible explanation for the disappointing results is that, in retrospect, patient selection could

have been better. During the same time period (2009-2013), only 50 FP bypasses were performed for CLTI in our unit and it is probably the case that a significant proportion of the CS patients who underwent PBA +/- BMS could, and arguably should have had VB, which we know from B1 is associated with better long-term clinical outcomes(172). There was probably another group of CS patients who underwent so-called “compassionate” endovascular intervention, but whose outcomes were so poor from such intervention that, arguably, their interests would have been best served by primary amputation or conservative treatment.

We must recognise the limitations of this study, firstly we are comparing randomised data with a retrospective case series, introducing selection bias to our results. Secondly, the retrospective data collection prevents the reporting of other important clinical measures, such as WIFi score, which are known to have a significant impact on clinical outcomes. Finally this study is unable to make conclusions on the likely effect of newer devices such as DCB, DES, atherectomy and covered stents; this comparison is between two cohorts undergoing similar interventions. It is important to note that there is no randomised data to support the hypothesis ‘the introduction of new technologies has facilitated superior clinical performance of endovascular treatment over vein bypass surgery’, in-fact drug eluting devices (paclitaxel) may have a negative impact on patient survival(23). To that end we will have to wait for the data from non-industry funded RCTs, such BASIL-2(14), BASIL-3(15) and BEST CLI(16), to establish which CLTI patients are best served by an endovascular intervention and whether in such patients the use of DCB/DES is clinically and cost-effective, which patients should be offered VB, and which should probably be treated without revascularisation

CONCLUSION

This study suggests that patients being treated with an indiscriminate endovascular first revascularisation strategy for CLTI experience worse long-term clinical outcomes compared to those treated within the B1 trial.

3.4 CONTEMPORARY (2009-2014) CLINICAL OUTCOMES AFTER FEMORO-POPLITEAL BYPASS SURGERY FOR CHRONIC LIMB THREATENING ISCHAEMIA (CLTI) ARE INFERIOR TO THOSE REPORTED IN THE UK BYPASS VERSUS ANGIOPLASTY FOR SEVERE ISCHAEMIA OF THE LEG (BASIL) TRIAL (1999-2004)

ABSTRACT

Introduction

Bypass surgery (BS) remains the "gold standard" revascularisation strategy in patients with chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease. The BASIL-1 trial showed that in CLTI patients who survived for 2 years or more, BS resulted in better clinical outcomes. Despite this, there has been an increasing trend towards an endovascular first approach to infra-inguinal CLTI. Our aim was to investigate whether changes in practice have impacted upon the clinical outcomes of BS in our unit ten years after BASIL-1.

Methods

Data for patients who underwent femoro-popliteal (FP) BS in BASIL-1 (1999-2004) were retrieved from trial case record forms. The comparator contemporary series (CS) comprised all patients undergoing FP BS for CLTI in our unit between 2009-2014. Demographic and clinical outcome data on CS patients were collected from the prospectively collected hospital electronic notes. Anatomic patterns of disease in the BASIL-1 and CS cohorts were scored using Bollinger and GLASS. Statistical analysis was performed in SAS v9.4.

Results

There were 128 BASIL-1 and 50 CS patients. Baseline age, gender, affected limb, and diabetes prevalence were similar, as were days spent in hospital out to 12 months and length of follow-up. BASIL-1 patients were more likely to be current smokers (p=0.000) and had a higher creatinine (p=0.04). The 30-day morbidity and mortality were higher in BASIL-1 (45.3% vs 22%, p=0.004). There was no significant difference between BASIL-1 and CS with regard to run-off Bollinger (37.7 v 32.1, p=0.167) and IP GLASS (0 vs 0, p=0.390) scores, with both groups having a median of 2 run-off vessels. Amputation free survival (62% vs 28%, HR 1.86, 95%CI 1.18-2.93, p=0.007), limb salvage (85% vs 69%, HR 2.31, 95%CI 1.14-4.68, p=0.02), overall survival (69% vs 35%, HR 1.66, 95%CI 1.00-2.74, p=0.05) and Major Adverse Limb Events (67% vs 47%, HR 1.93, 95%CI 1.15-3.22, p=0.01) were all significantly better in BASIL-1.

Conclusion

Although 30-day mortality and morbidity were significantly lower, all of the examined longer-term clinical outcomes after FP BS were significantly worse in the CS group a decade on from BASIL-1. Further research in the form of prospective cohort studies (PCS) and randomized controlled trials (RCT) is urgently required to determine if the CS data reported here are generalizable to current vascular surgical practice and, if so, to determine the reasons for these unexpected outcomes.

INTRODUCTION

Chronic limb threatening ischaemia (CLTI) is the most severe form of peripheral arterial disease (PAD) and is characterized by ischemic rest pain and/or tissue loss/gangrene(173, 174). The worldwide incidence of CLTI is increasing due to ageing and the growing incidence of diabetes mellitus and chronic kidney disease(6, 175). Despite recent advances in medical therapies and endovascular, surgical and hybrid revascularisation technologies and techniques, CLTI patients remain at high risk of cardiovascular mortality and morbidity, and limb loss(176). With regard to evidence-based revascularisation (EBR), the first UK NIHR HTA-funded Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL-1) trial remains the only published randomised controlled trial (RCT) to have compared a bypass surgery (BS) first with a plain balloon angioplasty (PBA) first approach to infra-inguinal revascularisation in CLTI(20). BASIL-1 showed that in patients likely to live for more than two years, overall (OS) and amputation free survival (AFS) were better following randomization to BS than to PBA. Despite this 'level 1' evidence in favour of BS over PBA, there has been a world-wide trend towards an endovascular first approach to the treatment of femoro-popliteal (FP) disease in patients with CLTI. Those advocating such an approach point to lower peri-procedural morbidity and mortality, and further claim that current best endovascular treatment (BET) results in far superior outcomes than those reported in BASIL(148, 149, 177). Although not evidence-based, in many vascular units around the world, BS is increasingly reserved for those patients who cannot have endovascular intervention or where such intervention has failed. Due to the lack of published contemporary series (CS) of BS for CLTI, the impact of such practice on outcomes following BS is unknown. The aim of the present study, therefore, is to

compare clinical outcomes following FP BS in a CS (2009-2014) from a single UK academic vascular unit with those reported in the BASIL-1 trial operated a decade earlier (1999-2004).

METHODS

The BASIL-1 trial randomised 452 patients presenting with CLTI due to infra-inguinal disease to either a BS-first or a PBA-first revascularisation strategy. The recruitment period was 1999 to 2004 and follow up ended on 1 July 2007(147). For the present analysis, the BASIL-1 cohort comprised trial patients undergoing primary FP BS with any conduit. The CS cohort comprised patients undergoing primary FP BS for CLTI with any conduit in our unit between 2009 and 2014 and follow-up ended on 31 May 2017. Within the CS study period (2009-2014), 132 FP BS were performed in our unit. Of these, 72 BS were for claudication (IC) or popliteal aneurysm disease and so were excluded; as were four contralateral BS and six secondary BS performed for failed endovascular interventions within the previous 12 months. This left 50 patients in the CS cohort undergoing primary FP BS for CLTI compared with 128 BASIL-1 patients.

The BASIL-1 and CS cohorts were compared in terms of baseline factors, 30-day mortality and morbidity, length of hospital stay out to 12 months and amputation-free survival (AFS), limb salvage (LS), overall survival (OS), and freedom from re-intervention (FFR) and major adverse limb events (MALE). FFR was defined as the absence of subsequent re-vascularization or intervention for any post-operative complications. Minor amputations were excluded as they were considered a consequence of the clinical presentation. Major amputation was defined as amputation above the ankle joint. Minor amputation includes amputation of single or multiple digits,

or trans-metatarsal amputation (no Chopart's or Lisfrank amputations were performed within the trial). MALE was defined as any ipsilateral limb intervention (excluding minor amputation) after initial intervention. Bollinger(164) and Global Vascular Guideline (GVG) GLASS grade and scores were used to quantify the pattern of anatomical disease prior to intervention.

GLASS score is a new anatomical staging system designed by an expert global panel as part of the Global Vascular Guidelines on Chronic Limb Threatening Ischaemia. GLASS is part of the Patient, Limb, Anatomy paradigm presented in the GVG. GLASS involves choosing the target artery pathway (TAP) for endovascular revascularisation from the origin of the SFA (common and deep femoral disease are considered part of "inflow" and considered corrected prior to more distal revascularisation) to the foot with the aim of establishing in-line flow. Disease severity in FP and IP segments are graded separately on features including length of disease, stenosis or occlusion and level of calcification. FP and IP grades are combined within a matrix to determine GLASS stage. GLASS stage is believed likely to correlate with endovascular immediate technical success rates and 12-month limb-based patency (LBP) GLASS has been presented at the European Society of Vascular Surgery, Lyon (France) 2017, and Society of Vascular Surgery VAM in San Diego (2017) and Boston (2018). The concept is that GLASS will act as an aid to shared-decision making and stratification within trials comparing different form of revascularisation. We understand that the the GVG on CLTI are likely to be published in EJVES and JVS supplement in Q4 of 2108.

Ethical approval was granted for the BASIL trial (ISRCTN – 45398889), no ethical approval was required for the CS data collection as this is classed as audit of clinical outcomes.

Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the cohorts were compared using t-test, chi-squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

RESULTS

Patient age, gender, and prevalence of diabetes were similar in both cohorts. BASIL patients were more likely to be current smokers, less likely to be on best medical therapy (BMT) and had a higher baseline creatinine (**Table 3.4.1**).

Immediate technical success rate, as judged by the operating surgeon, was very high in both the BASIL-1 (126/128, 98%) and CS (50/50, 100%) cohorts. Minor amputation rates were equivalent between the two cohorts (23.4% vs 20%, p=0.6) suggesting equivalent burden of tissue loss. BASIL-1 trial patients had a non-significantly longer mean (SD) index admission when compared to the CS patients (23.2 [26.3] vs 15.6 [20.3] days, p = 0.7). However, difference in cumulative inpatient hospital days by 12 months had virtually disappeared (24.2 [26.4] versus 27.3 [26.8] days, p = 0.5). BASIL-1 patients suffered significantly higher overall combined peri-operative (30-day) mortality and morbidity (45% vs 22%; p = 0.004), including higher rates of wound infection (p=0.02). However, there was no significant difference in major adverse cardiac events (MACE) (8% vs 2%, p=0.1) (**Table 3.4.2**).

Table 3.4.1 *Comparison of contemporary series (CS) and Bypass versus Angioplasty for Severe Ischaemia of the leg (BASIL) cohorts at baseline*

Demographic	Specific	BASIL (n = 128)	CS (n = 50)	P value
Conduit	Vein	89 (70%)	39 (78%)	0.3
	Prosthetic	39 (30%)	11 (22%)	
Distal Anastomosis	Above Knee	60 (47%)	7 (14%)	<0.0001
	Below Knee	68 (53%)	43 (86%)	
Sex	Male	78 (61%)	36 (72%)	0.2
Limb	Right	57 (45%)	29 (58%)	0.1
Age	Mean (SD)	71 (8.1)	71 (10.1)	0.8
Indication	Rest pain	52 (41%)	16 (32%)	0.3
	Tissue loss	11 (9%)	8 (16%)	
	Both	62 (48%)	26 (52%)	
	Data missing	3 (2%)	0 (-)	
Minor Amputation	Yes	30 (23.4%)	10 (20%)	0.6
Smoking status	Never	17 (13%)	8 (16%)	**<0.0001**
	Ex-Smoker	65 (51%)	23 (46%)	
	Current	46 (36%)	10 (20%)	
	Unknown	0 (-)	9 (18%)	
Diabetes Mellitus	Yes	47 (37%)	18 (36%)	0.9
Congestive Heart Failure	Yes	5 (4%)	6 (12%)	**0.04**
Hypertension	Yes	77 (60%)	41 (82%)	**0.006**
Coronary Artery Disease	Yes	35 (27%)	10 (20%)	0.3
Chronic Obstructive Airway Disease	Yes	19 (15%)	4 (8%)	0.2
Creatinine	Mean (SD)	125.6 (135.7)	85.3 (40.2)	**0.04**
Statin	Yes	39 (31%)	47(94%)	**<0.0001**

Anti-platelet	Yes	85 (66%)	41 (82%)	**0.04**
Anticoagulation	Yes	9 (7%)	10 (20%)	**0.01**
ACE inhibitor	Yes	24 (19%)	18 (36%)	**0.01**
Beta Blocker	Yes	13 (10%)	10 (20%)	**0.08**

ACE - Angiotensin Converting Enzyme
SD - Standard Deviation

Table 3.4.2 *Comparison of 30-day outcomes in the Bypass versus Angioplasty for Severe Ischaemia of the leg (BASIL) and contemporary series (CS) cohorts*

Complication	**BASIL (n = 128)**	**CS (n = 50)**	**P value**
Mortality (any cause	7 (5%)	1 (2%)	0.3
Overall morbidity and mortality combined	58 (45%)	11 (22%)	**0.004**
Angina	0 (-)	0 (-)	-
Myocardial infarction	5 (4%)	0 (-)	0.2
Transient ischaemic attack	0 (-)	0 (-)	-
Cerebrovascular accident	1 (1%)	0 (-)	0.5
Haematoma (not operated)	7 (5%)	2 (4%)	0.7
Haematoma (operated)	2 (2%)	1 (2%)	0.8
Wound infection	37 (29%)	6 (12%)	**0.02**
Lower respiratory tract infection	4 (3%)	1 (2%)	0.7
Upper respiratory tract infection	2 (2%)	0 (-)	0.4
False aneurysm (not operated)	1 (1%)	0 (-)	0.5
False aneurysm (Operated)	0 (-)	0 (-)	-

Any further surgical intervention	3 (2%)	4 (8%)	0.08
Major Adverse Cardiac Event	10 (8%)	1 (2%)	0.1

With regard to long-term clinical outcomes, AFS (62% vs 28%, HR 1.86, 95% CI 1.18-2.93, p=0.007), LS (85% vs 69%, HR 2.31, 95% CI 1.14-4.68, p=0.02), OS (69% vs 35%, HR 1.66, 95% CI 1.00-2.74, p=0.05) and MALE (67% vs 47%, HR 1.93, 95% CI 1.15-3.22, p=0.01) were all significantly better in the BASIL-1 cohort (**Figures 3.4.1-4**).

Figure 3.4.1 *Comparison of amputation free survival (AFS) in Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and contemporary series (CS) cohorts*

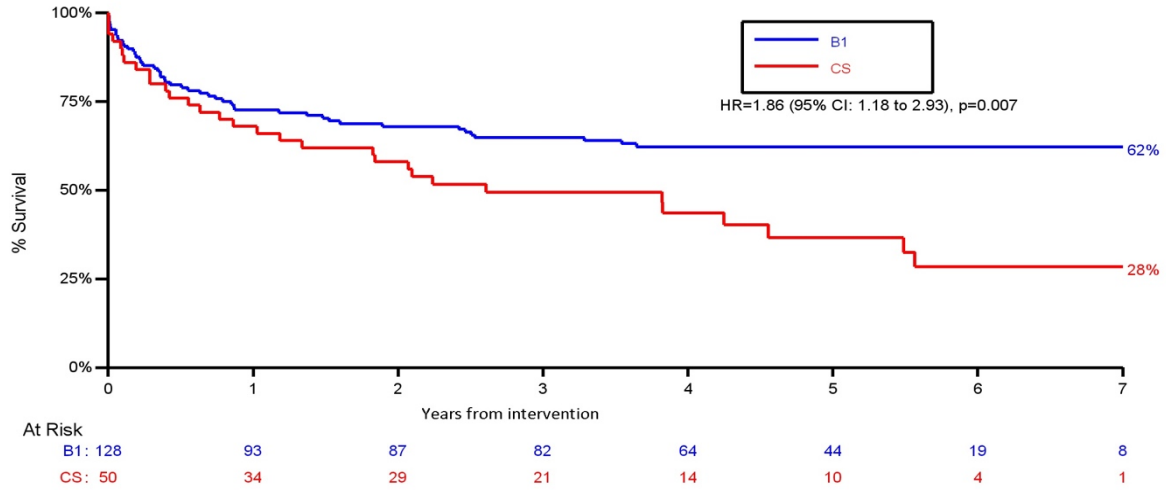


Figure 3.4.2 *Comparison of limb salvage in Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and contemporary series (CS) cohorts*

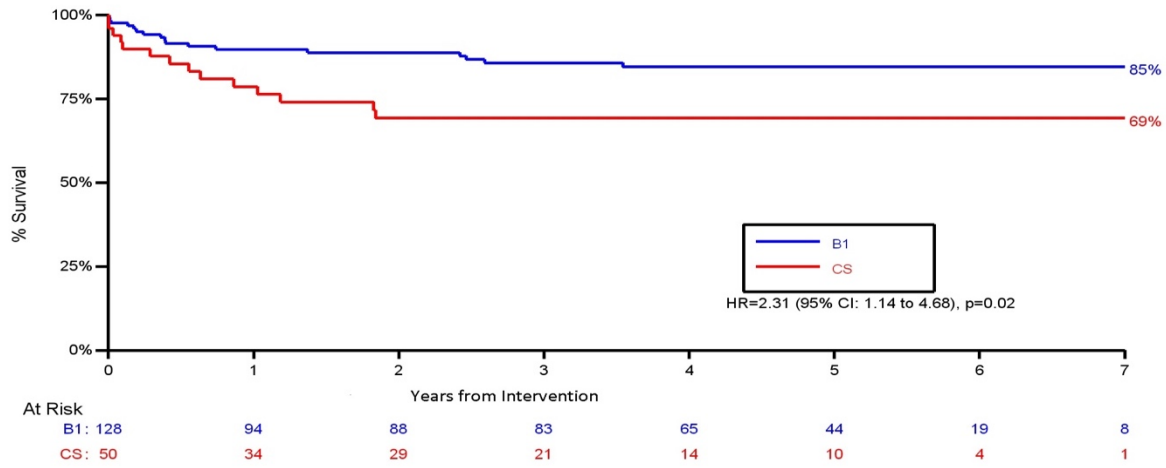


Figure 3.4.3 *Comparison of overall survival (OS) in Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and contemporary series (CS) cohorts*

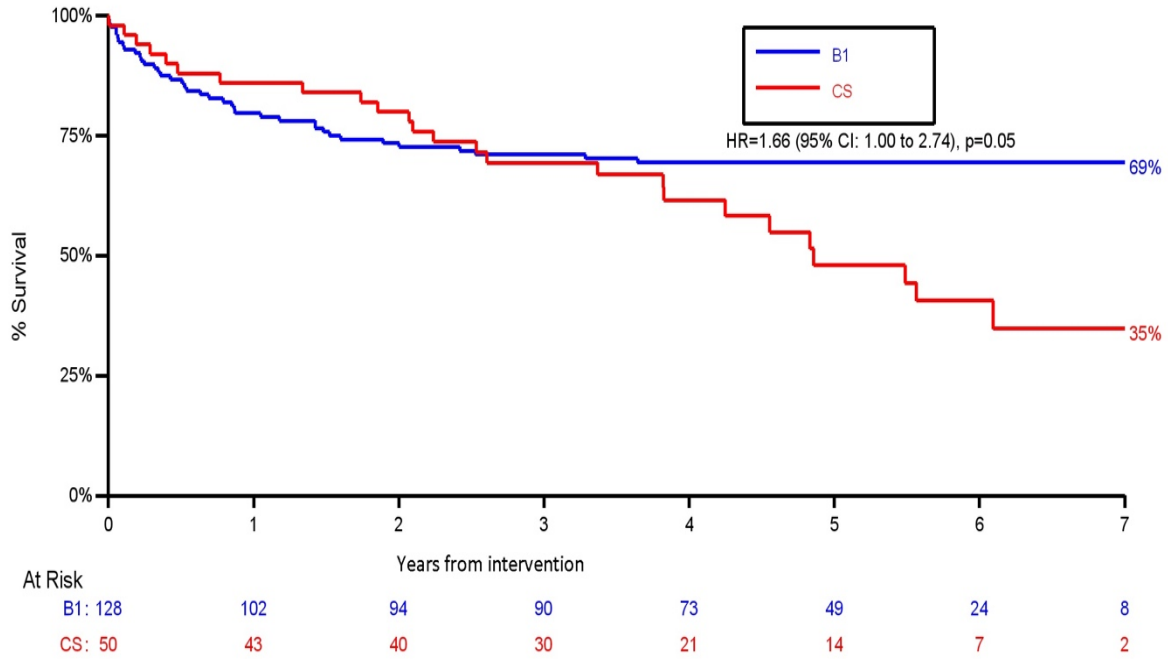
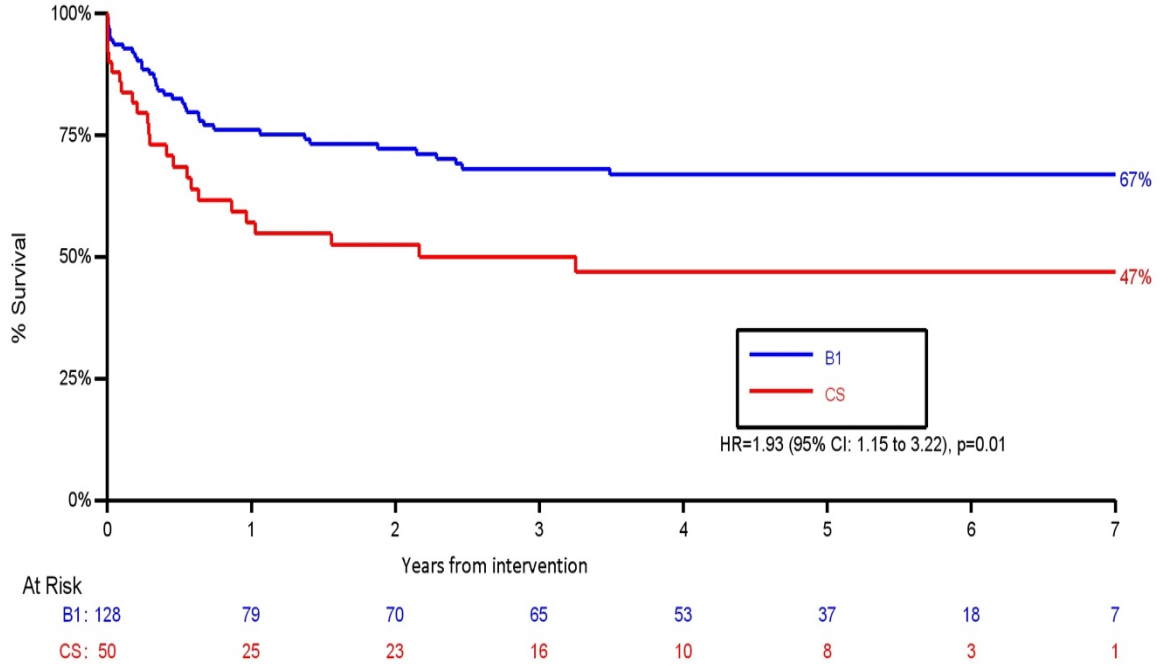
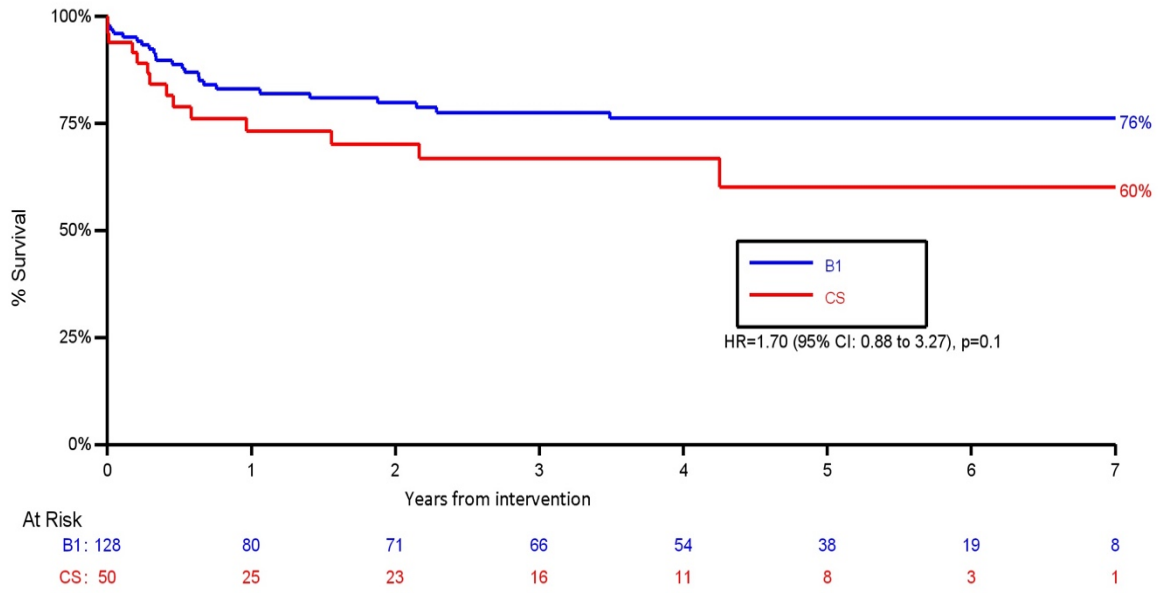


Figure 3.4.4 *Comparison of major adverse limb event (MALE) in Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and contemporary series (CS) cohorts*



FFR (76% vs 60%, HR=1.70, 95% CI 0.88 – 3.27, p=0.1) was non-significantly better in BASIL-1 when compared to the CS cohort (**Figure 3.4.5**).

Figure 3.4.5 *Comparison of freedom from reintervention (FFR) in Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and contemporary series (CS) cohorts*



In terms of anatomic burden of disease, there was no significant difference between BASIL-1 and CS with regard to run-off Bollinger score (37.7 vs 32.1, p=0.167) and IP GLASS (0 vs 0, p=0.390) grade, with both groups having a median of 2 run-off vessels. Nor was there any difference between total Bollinger score (63.1 vs 65.4, p=0.926). However, patients in the CS had a significantly higher FP GLASS score (3 vs 4, p=0.000) (**Table 3.4.3**).

Table 3.4.3 *A comparison of anatomical disease using Bollinger score between the Bypass versus Angioplasty for Severe Ischaemia of the leg (BASIL) and contemporary series (CS) cohorts*

		BASIL	CS	P value
Total Bollinger Score	Mean (SD)	63.1(23.4)	65.4(28.5)	0.926
Total run off Bollinger Score (above knee bypass)	Mean (SD)	40.8(25.1)	27.1(27.5)	0.189
Total run off Bollinger Score (Below knee bypass)	Mean (SD)	35.0(18.5)	33 (22.6)	0.623
Total run off Bollinger Score (combined)	Mean (SD)	37.7(21.9)	32.1(23.1)	0.167
Number of run off vessels	Median (IQR)	2 (1-2)	2 (1-3)	0.051
FP GLASS	Median (IQR)	3 (2-4)	4 (4-4)	0.000
IP GLASS	Median (IQR)	0 (0-0)	0 (0-0)	0.390
Possible Target Artery	AT (N)	48	26	0.105
	PT (N)	34	21	0.083
	PP (N)	66	25	0.544

CS - Contemporary Series
FP – Femoro-popliteal
IP – Infra-popliteal
AT - Anterior Tibial Artery
PT - Posterior Tibial Artery
PP - Peroneal Artery
SD - Standard Deviation
IQR - Inter-Quartile Range

DISCUSSION

In the present study, although peri-operative (30-day) mortality and morbidity were significantly lower, long-term clinical outcomes following primary FP BS for CLTI in our unit between 2009 and 2014 were significantly worse than those reported in the BASIL-1 trial a decade earlier (1999-2004). Further research is required to determine if the CS data reported here are generalizable to current vascular surgical practice and, if so, to determine the reasons for these unexpected data. Possible causes

include a loss of surgical skills as a result of the overall reduction in open vascular procedures and/or a tendency to reserve BS for patients considered unsuitable for endovascular intervention due the severity of their tissue loss and/or the extent and complexity of their underlying disease(27, 138, 178, 179). While loss of surgical skills is certainly possible, this does not appear to be supported by the observation that CS patients had lower overall 30-day mortality and morbidity as well as a trend towards a shorter index admission(180-183). With regard to the clinical severity of disease, the proportion of patients with tissue loss was similar in the two cohorts. We were unable to determine the extent of tissue loss in the CS patients with same precision as was the case in BASIL-1. However, using rates of minor amputation as a surrogate, it would seem that the severity of tissue loss was broadly similar in both groups. With regard to anatomic complexity of disease, the Bollinger scoring and GLASS grade would suggest a similar disease burden. Importantly the run off scores were almost identical for both groups suggesting that the outflow for bypass surgery was equivalent. Post procedural surveillance may have been different between the two cohorts. Surveillance post bypass was not prescriptive in BASIL-1, its use was not recorded and re-intervention was largely clinically driven. In the CS only 15 patients were enrolled in formal ultrasound graft surveillance, none had formal haemodynamic surveillance. As such, it is possible that differences in post bypass care could contribute to the difference in clinical outcomes observed.

An important question is the degree to which our practice and the outcomes reported here can be generalized more widely to current vascular and endovascular practice within the UK and elsewhere. Like many units, despite a lack of evidence indicating that endovascular intervention offers a more clinically effective and cost-effective option for CLTI patients who could have a vein bypass, and growing evidence that

failed endovascular intervention compromises outcomes following subsequent BS, we have increasingly employed an endovascular first approach to the management of CLTI. Thus, during the study period (2009-2014), almost five times more (n = 237) patients had a FP endovascular intervention for CLTI than had BS (n = 50). In the UK, virtually all CLTI patients are managed within the National Health Service (NHS), where care is provided free at the point of delivery to all UK and European Union citizens, by salaried vascular surgeons and interventional radiologists. As such, the "turf battles" and re-imbursement issues seen elsewhere in the world are largely irrelevant to UK practice. Rather, the main reason for our endovascular preference is probably a reluctance to subject elderly and co-morbid patients to prolonged surgery and, linked to that, a belief that an endovascular approach is associated with less resource utilization in terms of operating theatre time and bed days in hospital. However, these beliefs are not supported by hard data and we have to accept that our current practice may not be maximizing long-term clinical outcomes for the greatest number of our CLTI patients.

Interestingly, in the UK, Heikkila et al.(184) have recently published 1-year outcomes following lower limb revascularisation using data from the national vascular registry (NVR), hospital episode statistics (HES), and the office of national statistics (ONS). The authors conclude that overall survival and amputation rates have significantly improved over a 10-year period. They suggest that one reason for the observed improvement may be centralization of services due to increased specialization in vascular surgery. These UK national data would seem to starkly contradict those reported here from a single UK academic vascular unit. However, it must however be noted that Heikkila and colleagues grouped together a wide range of surgical and endovascular procedures, studies patients with CLTI and intermittent claudication (IC),

and that their follow-up was short. Unfortunately, at the present time, there are very few other published data with which we can compare our own long-term outcome data. Thus, most surgical and endovascular CLTI cohorts reported in the literature have limited follow-up and/or mix CLTI with IC and/or mix FP with infra-popliteal (IP) procedures which makes interpretation of the data extremely difficult(21, 131, 185).

In summary, therefore, there is a clear and urgent need to perform further RCTs to determine the pros and cons of a BET-first versus a BS-first revascularisation strategy in sub-groups of CLTI patients presenting with different degrees of tissue loss and anatomic complexities of disease. To this end, in the UK, NIHR HTA is funding the BASIL 2(14) and BASIL 3(15) to inform practice in IP disease and the impact of drug eluting technologies in the FP segment respectively. In the US, NIH have funded the BEST-CLI(16) trial. Together, these on-going trials will report contemporary clinical outcomes in several thousand patients undergoing BET and BS for CLTI and inform EBR decisions going forward.

CONCLUSION

Although 30-day mortality and morbidity were significantly lower, all of the examined longer-term clinical outcomes after FP BS were significantly worse in the CS group a decade on from BASIL-1.

3.5 A COMPARISON OF CONTEMPORARY OUTCOMES AFTER FEMORO-POPLITEAL PLAIN BALLOON ANGIOPLASTY AND FEMORO-POPLITEAL BYPASS SURGERY

ABSTRACT

Introduction

Despite the BASIL-1 trial concluding that bypass surgery (BS) was superior to plain balloon angioplasty (PBA) in terms of longer-term amputation free (AFS) and overall survival (OS), CLTI patients are increasingly offered an endovascular-first revascularisation strategy. This study investigates whether the results of BASIL-1 are still relevant to current practice by comparing femoro-popliteal (FP) BS with PBA in a series of CLTI patients treated in our unit ten years after BASIL-1 (1999-2004).

Methods

We retrospectively analysed prospectively gathered hospital data pertaining to 279 patients undergoing primary FP BS or PBA for CLTI in the period 2009 to 2014. We report baseline characteristics, 30-day morbidity and mortality, major adverse cardiovascular events (MACE) and long-term AFS, limb salvage (LS), OS, major adverse limb events (MALE), and freedom from re-intervention (FFR).

Results

234 (84%) and 45 (16%) patients underwent PBA and BS respectively. PBA patients were significantly older (77 vs 71 years, p=0.001) and more likely to be female (45% vs 28%, p=0.026). Bollinger and GLASS anatomic scores were significantly more severe in the BS group. Technical success was better for BS (100% vs 87%, p=0.007). Index hospital stay was shorter for PBA (9.1 vs 15.6 days, p=0.035) but there was no

difference in hospital days or admissions over the next 12 months. AFS (HR 1.00), LS (HR 1.44), OS (HR 0.81), MALE (HR 1.25) and FFR (HR=1.00) were not significantly different between PBA and BS.

Conclusion

Important clinical outcomes following FP BS and PBA for CLTI have not changed significantly in our unit in the 10 years following the BASIL-1 trial. BASIL-1 therefore remains relevant to our current practice and should inform our approach to the management of CLTI going forward.

INTRODUCTION

Chronic limb threatening ischaemia (CLTI) is an increasing global health and social care problem, mainly due to tobacco use and the increasing worldwide prevalence of diabetes(25)[1]. Despite this, the evidence base informing preferred revascularization strategies in CLTI remains extremely poor(186). The UK Bypass versus Angioplasty for Severe Ischaemia of the Leg trial (BASIL-1) trial remains the only published randomised control trial (RCT) to have compared infra-inguinal bypass surgery (BS) with plain balloon angioplasty (PBA) in patients with chronic limb threatening ischaemia (CLTI)(137). BASIL-1 showed that in patients living more than 2 years, a BS first revascularisation strategy was associated with better amputation free (AFS) and overall survival (OS)(20). Furthermore, the immediate technical and early clinical failure rate of PBA was higher than with BS, and many patients randomised to PBA had to cross-over to BS(141, 152). BS performed after failed PBA was associated with worse outcomes than primary BS. Furthermore, in an infra-popliteal (IP) BASIL-1 sub-group analysis, BS was associated with better quality of revascularisation in terms of relief of ischaemia rest pain(21). So, the only available 'level 1' evidence strongly suggests that endovascular intervention should normally be reserved for those CLTI patients who cannot have vein BS. Despite this, patients with CLTI are increasingly offered primary endovascular intervention(92). This non-evidence-based trend is often justified on the grounds that the current results of endovascular treatment are likely to be better than those observed in BASIL-1 in whch procedures were performed between 1999 and 2004. This view has to a significant extent been based on the belief that drug coated balloons (DCB) and drug eluting stents (DES) provide superior clinical outcomes when compared to PBA and bare metal stents (BMS); even

though there is no evidence for that in the CLTI population, and in fact the opposite appears be true(23, 187, 188). Indeed, there are significant on-going safety concerns associated with the use of paclitaxel DCB and DES (23, 188) such that regulatory authorities have felt the need to issue advice regarding their use (189, 190) and on-going RCTs evaluating these devices intermittently had their recruitment paused(15, 191). Nevertheless, like many vascular units, we have increasingly used primary endovascular revascularization (in the form of PBA +/- BMS) for CLTI on the grounds that it is assumed to be quicker and easier for patients than BS, at least in the short-term. It is also logistically much easier to deliver timely PBA than it is BS in an increasingly stretched UK National Health Service (NHS). However, a critical internal review of our practice and outcomes suggests that our growing enthusiasm for an endovascular first revascularisation strategy where possible in patients presenting with CLTI, based on these considerations, and also a belief that the results of endovascular revascularisation have improved since BASIL-1, may have been misguided(172, 192, 193). The aim of the present study, therefore, was to further investigate whether the results of BASIL-1 are still relevant to our current practice by comparing femoro-popliteal (FP) BS with PBA in a series of CLTI patients treated in our unit between 2009 and 2014, ten years after BASIL-1.

METHODS

We retrospectively analysed prospectively gathered hospital electronic data pertaining to a contemporary series (CS) of patients undergoing FP BS or PBA for CLTI between 1 January 2009 and 31 December 2014, ten years on from the BASIL-1 recruitment period. Inclusion criteria were the same as for the on-going BASIL-3 trial(15). In

patients undergoing bilateral revascularisation during the study period, the first leg undergoing attempted revascularisation was designated as the index leg. Patients who had undergone an intervention for CLTI in the index leg within the previous 12 months were excluded. We report baseline characteristics including Bollinger(164) and GLASS(25) anatomic scores, 30-day morbidity and mortality, major adverse cardiovascular events (MACE), and long-term amputation free survival (AFS), limb salvage (LS), overall survival (OS), major adverse limb events (MALE), and freedom from re-intervention (FFR). Major amputation was defined as any above ankle amputation of the index limb. FFR patients were those who did not undergo any subsequent attempted revascularisation of the index leg during the study period and did not return to theatre for complications. Minor amputation was not considered as a re-intervention as we took the view that this was a likely consequence of the severity of the presenting disease rather than the type of primary revascularisation. MALE was defined as any return to theatre for complications, any further attempt at revascularisation, or any major amputation during the study period in respect of the index limb. MACE was defined as myocardial Infarction (MI), coronary revascularisation, transient ischaemic attack (TIA), cerebrovascular accident (CVA) or death within 30 days of the primary index revascularisation.

Ethical approval was not required for this study as is was deemed as a service outcomes audit.

Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the cohorts were compared using t-test, chi-squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

There were 234 (84%) and 45 (16%) patients who underwent PBA and BS respectively (**Table 3.5.1**). PBA patients were significantly older (77 vs 71 years, p=0.00) and more likely to be female (28% vs 45%, p=0.026). Rates of tissue loss and baseline medical status were similar between the two groups. Fewer patients in the PBA group were receiving best medical therapy (BMT) (**Table 3.5.2**).

Table 3.5.1 *A comparison of baseline demographics between patients undergoing femoro-popliteal bypass and femoro-popliteal plain balloon angioplasty*

DEMOGRAPHIC	SPECIFIC	CS Endo	CS Bypass	P VALUE
N		234	45	
SEX	MALE	127 (54%)	34 (76%)	0.008
LIMB	RIGHT	109 (47%)	27 (60%)	0.1
AGE	MEAN (SD)	76.9 (11.1)	70.0 (9.9)	0.0001
INDICATION	RP	73 (31%)	15 (33%)	<0.0001
	TL	131 (56%)	8 (18%)	
	BOTH	30 (13%)	22 (49%)	
SUCCESS	YES	204 (87%)	45 (100%)	0.007
INDEX DAYS	MEAN (SD)	9.0 (13.6)	16.4 (21.2)	0.003
12 MONTH HOSPITAL DAYS	MEAN (SD)	23.9 (30.9)	26.0 (27.1)	0.5
IP DAYS TO PRIMARY END POINT	MEAN (SD)	39.3 (36.6)	40.4 (33.6)	0.8
ADMISSIONS O PRIMARY ENDPOINT	MEAN (SD)	5.1 (4.8)	5.7 (7.1)	0.5
CREATININE	MEAN (SD)	107.4 (106.7)	84.0 (36.7)	0.1
SMOKER	NEVER	25 (11%)	8 (18%)	<0.0001
	EX-SMOKER	25 (11%)	7 (15%)	
	CURRENT	34 (14%)	22 (49%)	
	UNKNOWN	150 (64%)	8 (18%)	
DIABETES MELLITUS	YES	84 (36%)	17 (38%)	0.8

CONGESTIVE HEART FAILURE	YES	23 (10%)	6 (13%)	0.4
HYPERTENSION	YES	151 (65%)	36 (80%)	0.04
CORONARY ARTERY DISEASE	YES	57 (24%)	10 (22%)	0.8
COPD	YES	27 (12%)	4 (9%)	0.6

N - Number
SD - Standard Deviation
RP - Rest Pain
TL - Tissue Loss

Table 3.5.2 *A comparison of medical therapy between patients underogoing femoro-popliteal bypass and femoror-popliteal plain balloon angioplasty*

MEDICINE	SPECIFIC	FP BYPASS	CS BYPASS	P VALUE
N		234	45	
STATIN	YES	145 (62%)	42(93%)	0.0002
LIPID	YES	10 (4%)	1 (2%)	0.2
ANTPLATELET	YES	162 (65%)	36 (80%)	0.08
ANTICOAGULATION	YES	29 (12%)	9 (20%)	0.1
ACE	YES	98 (42%)	16 (36%)	0.1
BETA BLOCKER	YES	55 (24%)	9 (20%)	0.2

N - Number

Immediate technical success was better for BS than PBA (100% vs 87%, p=0.007). Index hospital stay was shorter for PBA than BS (9.1 vs 15.6 days, p=0.035). There was no difference in the number of hospital days or admissions out to 12 months, or until primary endpoint. Morbidity and mortality out to 30-days were similar except for MACE, which was lower after BS (2% vs 13.5%, p=0.021) (**Table 3.5.3**). The anatomic extent and severity of arterial disease was significantly worse in the BS as demonstrated by Bollinger and GLASS (**Table 3.5.4**).

Table 3.5.3 *30 day complication between patients undergoing femoro-popliteal bypass and femoro-popliteal plain balloon angioplasty*

COMPLICATION	SPECIFIC	CS Endo	CS BYPASS	P VALUE
N		234	45	
MI	YES	12 (5%)	0 (-)	0.2
TIA/CVA	YES	14 (6%)	0 (-)	0.1
SURGICAL INTERVENTION	YES	17 (7%)	4 (9%)	0.8
AMPUTATION	YES	12 (5%)	3 (7%)	0.7
30 DAY MORTALITY	DEATH	9 (4%)	1 (2%)	1.0
30 DAY MORBIDITY & MORTALITY	YES	57 (24%)	8 (18%)	0.3
MACE	YES	32 (14%)	1 (2%)	0.03

N - Myocardial Infarction
TIA - Transient Ischaemic Attack
CVA - Cerebrovascular Accident

Table 3.5.4 *Bollinger and GLASS score difference between patients undergoing femoro-popliteal bypass and femoro-popliteal plain balloon angioplasty*

BOLLINGER	SPECIFIC	CS Endo	CS BYPASS	P VALUE
N		234	45	
Total Score	Mean (SD)	61 (31.5)	65 (27.2)	0.4
FP Score	Mean (SD)	22 (11.3)	34 (10.8)	<0.0001
IP Score	Mean (SD)	39 (28.2)	32 (23.1)	0.08
FP GLASS	Median (IQR)	4 (3-4)	4 (4-4)	0.001
0	N	0	1	<0.0001
1	N	13	0	
2	N	29	3	
3	N	60	2	
4	N	132	36	
Missing	N	0	3	
IP GLASS	Median (IQR)	0 (0-1)	0 (0-0)	0.2
0	N	164	32	0.0004
1	N	15	7	
2	N	22	3	
3	N	11	0	
4	N	22	0	
Missing	N	0	3	
Run Off Vessels	Median (IQR)	1 (1-2)	1 (1-2)	0.8

N	-	Number
FP Score	-	Femoro-popliteal Score
IP Score	-	Infra-popliteal Score
SD	-	Standard Deviation
IQR	-	Interquartile Range

Out to 7 years AFS (28% vs 29%, HR 0.96, 95% CI 0.64-1.45, p=0.8), LS (76% vs 73%, HR 1.26, 95% CI 0.65-2.44, p=0.5), OS (34% vs 29%, HR 0.81, 95% CI 0.52-1.27, p=0.4), MALE (50% vs 50.0%, HR 1.16, 95% CI 0.71-1.88, p=0.6) and FFR (58% vs 62%, HR=0.96, 95% CI 0.52 – 1.77, p=0.9) was not significantly different between the PBA and BS groups (**Figure 3.5.1-5**).

Figure 3.5.1 *Comparison of Amputation Free Survival following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb threatening ischaemia in a series of patients treated 2009-2014*

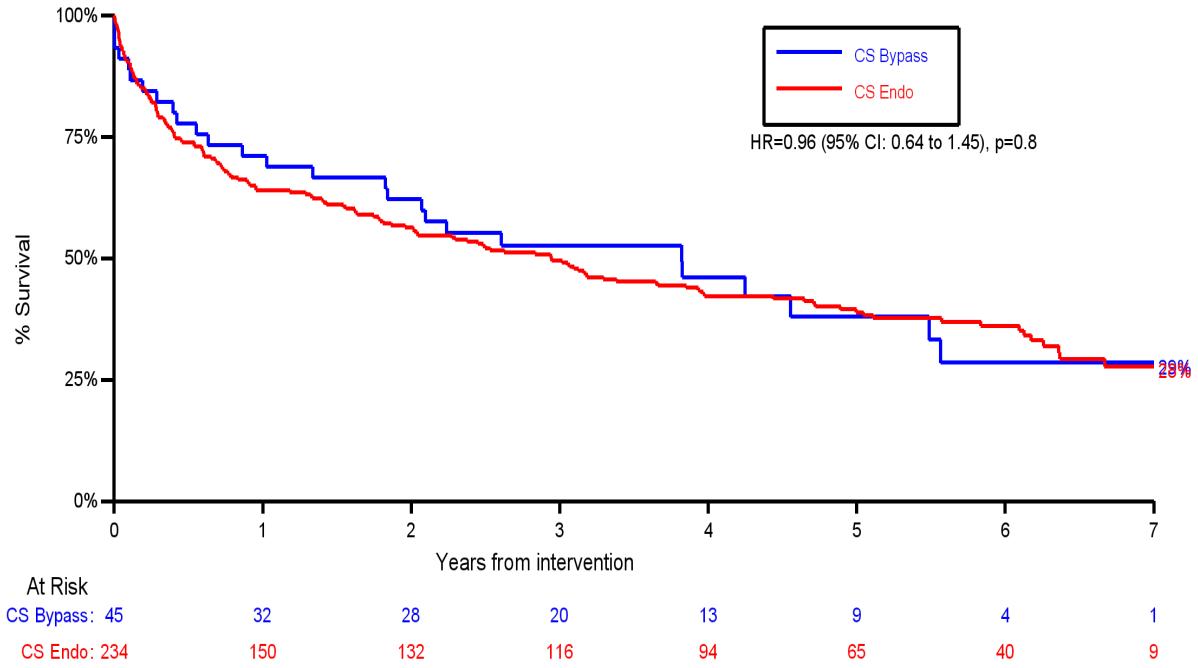


Figure 3.5.2 *Comparison of Limb Salvage following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb threatening ischaemia in a series of patients treated 2009-2014*

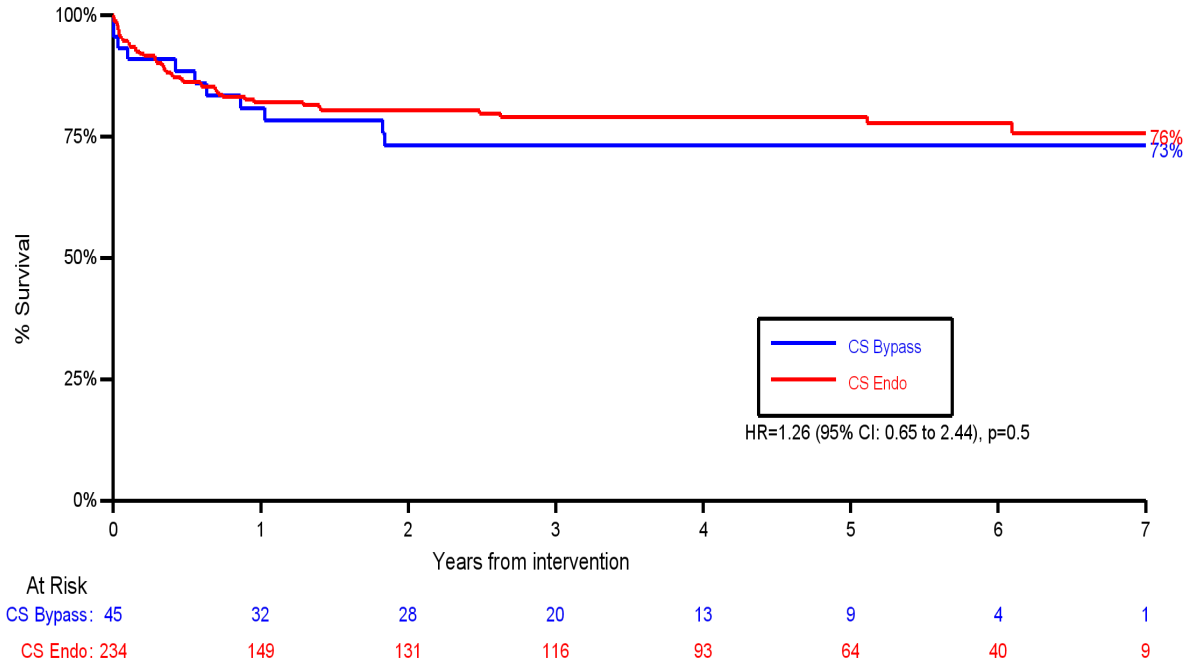


Figure 3.5.3 *Comparison of Overall Survival following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb threatening ischaemia in a series of patients treated 2009-2014*

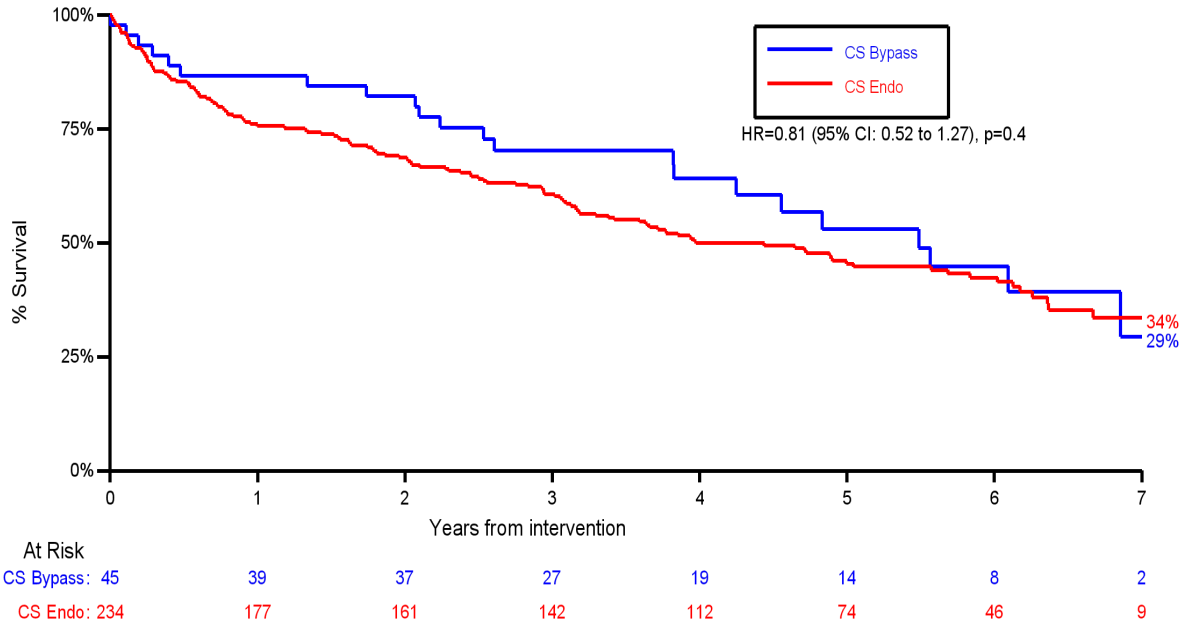


Figure 3.5.4 *Comparison of Freedom From Re-intervention following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb threatening ischaemia in a series of patients treated 2009-2014*

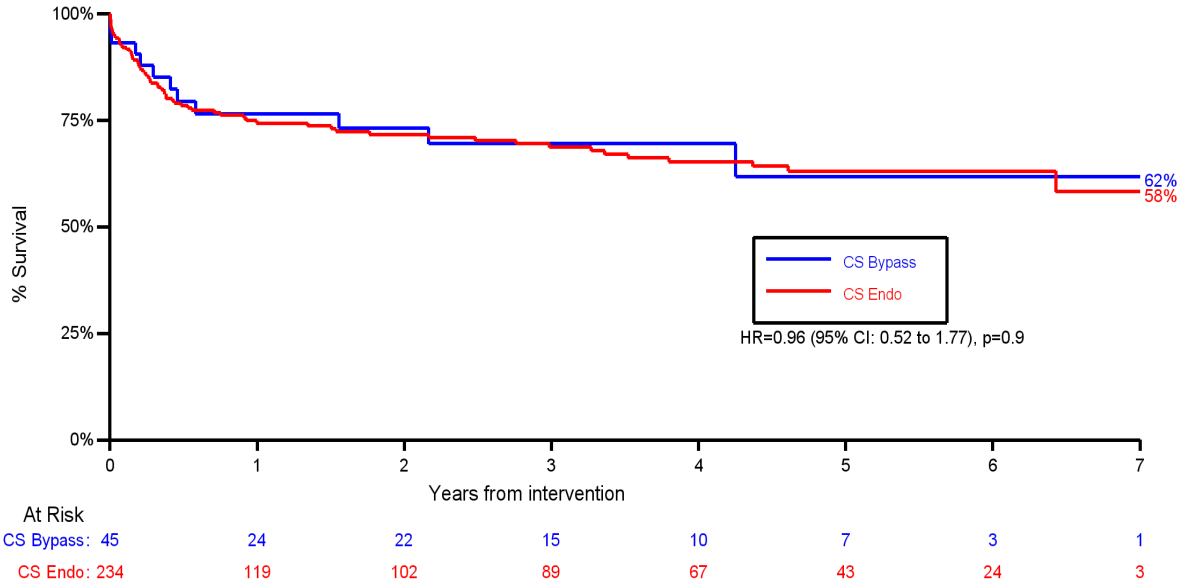
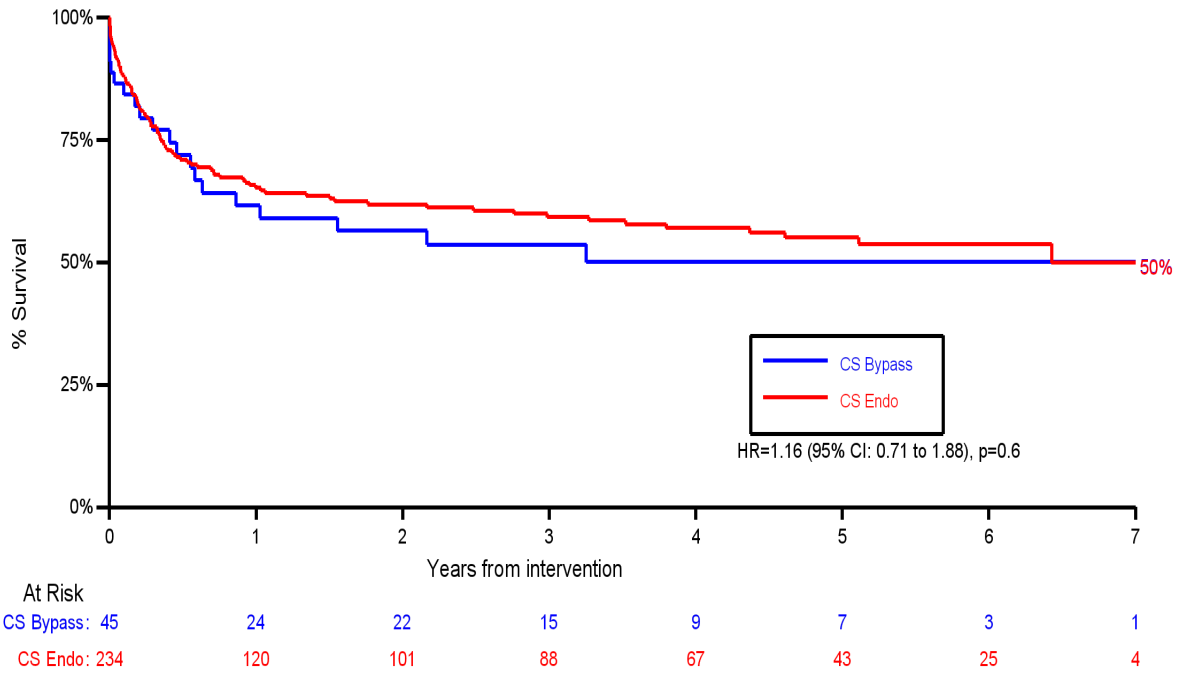


Figure 3.5.5 *Comparison of Major Adverse Limb Events following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb threatening ischaemia in a series of patients treated 2009-2014*



There was no significant difference between BASIL-1 and CS with regard to run-off Bollinger (39 vs 32, p=0.08) and IP GLASS (0 vs 0, p=0.2) grade, with both groups having a median of 1 run-off vessels to the foot (p=0.8). Nor was there any difference between total Bollinger score (61 vs 65, p=0.4). However, patients in the BS group had significantly more FP GLASS grade 4 disease (p=0.001) (**Table 3.5.4**).

DISCUSSION

Our key conclusion from this study is that important short, medium and long-term clinical outcomes following FP BS and PBA for CLTI in our unit have not changed significantly, in either absolute or relative terms, in the 10 years following the BASIL-1 trial. We believe, therefore, that the results and conclusions of BASIL-1 remain relevant to our current practice and should inform our preferred revascularisation strategies for CLTI. Specifically, current and other previously published data do not support the mantra that improvements in endovascular technologies and expertise have translated into better longer-term clinical outcomes for patients with CLTI since patients were randomised in BASIL-1(21, 141, 172, 192, 193).

Although comparison between RCT data (BASIL-1) and contemporary data are limited we have shown in our previous publications that contemporary clinical outcomes in both PBA and BS in the FP segment are significantly worse now than those observed in BASIL-1. In patients undergoing BS, both survival (HR 1.66, 95%CI 1.00-2.74, p=0.05) and limb-based outcomes (MALE, HR 1.93, 95%CI 1.15-3.22, p=0.01) were significantly worse in the contemporary series(172). Survival in those undergoing contemporary endovascular intervention was inferior to that observed in BASIL-1 (HR

= 0.58, 95% CI: 0.44 to 0.76, p = 0.0001) while there was no improvement in limb-based outcomes (MALE, HR=1.02, 95% CI: 0.76 – 1.37, p=0.9)(194).

In this study those treated with BS had significantly worse FP Bollinger and GLASS scores, suggesting an increased burden of disease in those patients treated with BS. Interestingly there was not a significant difference in disease burden compared to those treated in BASIL-1. Thus, the severity and complexity of disease treated has not worsened in this time. This supports the hypothesis that in our centre only those patients who are deemed very unlikely to have successful endovascular intervention are being considered for BS.

Although out to seven years clinical outcomes are equivalent, in terms of survival, there seems to be a trend to improved mid-term survival for patients undergoing BS. This may be as a result of more comprehensive use of so-called best medical treatment (BMT) (statin therapy 93% vs 62%, p=0.0002, antiplatelet therapy 80% vs 65%, p=0.08), or the older age of the patients in the PBA group. However, interestingly this trend was not observed when comparing the CS against the B1 cohort.

We must recognise the limitations of this study; the bypass group has small numbers (although reflective of the general spread of interventions in most centres) and may under/overestimate treatment effect. Single centre studies are limited by local practise, expertise and pressure on healthcare resources, questioning generalisability. Finally, the only endo intervention considered here was PBA +/- bailout BMS, in many other countries atherectomy and drug eluting devices are used as standard practise and may provide different results (although no independent randomised data supports this as yet).

It seems likely, therefore, that were BASIL-1 to be repeated now, similar results would probably be obtained and conclusions drawn. In other words, what evidence we have suggests that endovascular intervention should still be reserved for those patients who are not suitable for BS either because they do not have an adequate venous conduit or because they have co-morbidities that are thought to preclude open surgery. The clinical superiority of BS over endovascular intervention appears to be especially marked in patients with advanced limb threat(27) as well in those where the target artery path (TAP) is heavily diseased(47). The results of RCTs such BASIL-2, BASIL-3, and BEST-CLI(14-16), where patients can be stratified by level of limb threat and anatomic severity of disease, are urgently required to improve the evidence base underpinning the management of CLTI.

CONCLUSION

In terms of our own practice, current and other previously published data from our unit have led us to conclude that our revascularisation pendulum has swung too far in favour endovascular therapy. Specifically, a five to one ratio in favour of PBA versus BS no longer looks appropriate.

3.6 EVALUATION OF THE GLOBAL LIMB ANATOMIC STAGING SYSTEM IN PATIENTS WITH CHRONIC LIMB THREATENING ISCHAEMIA UNDERGOING ENDOVASCULAR INTERVENTION FOR FEMORO-POPLITEAL DISEASE

ABSTRACT

Background

Global Limb Anatomic Staging System (GLASS) is a new method of quantifying the anatomic severity of infra-inguinal disease in patients with chronic limb threatening ischaemia (CLTI). However, as GLASS has undergone limited validation, its value as an aid to shared decision making regarding the choice of revascularisation strategy remains incompletely defined. Here we report the relationship between GLASS and outcomes in a contemporary series (CS) comprising all 309 patients who underwent an attempt at femoro-popliteal (FP) and/or infra-popiteal endovascular therapy (EVT) for CLTI in our unit between 2009 and 2014.

Methods

Baseline patient characteristics and outcome data including immediate technical success (ITS), amputation free survival (AFS), overall survival (OS), limb salvage (LS), freedom from re-intervention (FF-R) and freedom from major adverse limb events (FF-MALE) were obtained from hospital databases. GLASS grades and stage were obtained from pre-EVT angiographic imaging. Outcome data were censored on 31 May 2017.

Results

Baseline patient characteristics were similar across different GLASS FP and IP grades and overall limb stages. Worsening GLASS stage was associated with a significant reduction in ITS (97.5% vs 91.5% vs 84.0%, p=0.029). At 72 months FF-R (HR 2.00, 95% CI 1.11 – 3.57, p=0.020) and FF-MALE (HR 1.76, 95% CI 1.10 – 2.81, p=0.019) were significant worse in GLASS stage 3 than in stage 2 limbs.

Conclusion

In our study there were significant differences in ITS, FF-R and FF-MALE between limbs with GLASS stage 2 and 3 disease. However, further GLASS refinement seems likely to be required if its utility in everyday clinical practice as an aid to shared decision making regarding choice of revascularisation strategy is to be maximised.

INTRODUCTION

The Global Vascular Guidelines (GVG) were published in June 2019 with the aim of promoting an evidence-based approach to the management of patients with chronic limb threatening ischaemia (CLTI) across the world(25, 26). The GVG proposed the Global Limb Anatomic Staging System (GLASS) as a new method for assessing the anatomic extent and complexity of infra-inguinal disease based on the evaluation of angiograms. The GLASS process begins by identifying a target artery path (TAP) which represents the route of endovascular therapy (EVT) considered most likely to provide continuous in-line flow to the foot. Below the knee, unless angiosome based revascularisation is being attempted, the TAP will usually include the least diseased crural artery. GLASS begins at the superficial femoral artery (SFA) origin as the common and deep femoral arteries are considered inflow vessels. Femoro-popliteal (FP) and infra-popliteal (IP) segments are considered separately and graded from 1 (least severe) to 4 (most severe). Severe calcification increases the FP/IP segment grade by 1. There is also a pedal modifier based on the status of the pedal arch. FP and IP grades are combined to provide a GLASS stage I (least severe) to III (most severe) for the whole limb. GLASS stages are designed to correspond to low, intermediate and high complexity EVT cases. The intention is that GLASS will act as an aid to shared decision-making regarding choice of revascularisation strategy by helping to predict immediate technical success (ITS) and 1-year limb-based patency (LBP) of the TAP following EVT. Our first attempt at GLASS evaluation was based on angiograms and outcome data from the UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) trial(47, 137). We concluded that GLASS

score was useful in predicting medium to long term limb-based outcomes in patients undergoing EVT, but not bypass surgery. However, as BASIL-1 patients were treated between 1999 and 2004, it has been suggested that, given the more recent advances in endovascular technologies and techniques, the relationships between GLASS and outcomes following EVT may have changed. In response to this suggestion, we now report the relationship between GLASS and clinical outcomes in a prospectively documented, contemporary series (CS) of all patients undergoing an attempt at FP EVT for CLTI in our unit between 1 January 2009 and 31 December 2014, which is ten years later than the BASIL-1 recruitment period(194).

METHODS

The present study includes 309 consecutive CLTI patients who underwent a primary attempt at FP and/or IP EVT as their first revascularisation procedure in a single vascular unit between 1 January 2009 and 31 December 2014. Only patients' primary intervention was included for analysis, repeat interventions on the treatment leg were defined as a re-intervention, contralateral limb interventions were excluded. Baseline patient and clinical outcome data (immediate technical success, ITS; amputation free survival, AFS; overall survival, OS; limb salvage, LS; freedom from re-intervention, FF-R; and freedom from major adverse limb events, FF-MALE) were obtained from prospectively gathered hospital records and databases. Outcome data were censored on 31 May 2017. ITS was contemporaneously recorded at the time of the EVT by the senior responsible interventionalist based upon successful device use and satisfactory post-intervention angiographic appearances. Those patients where the intervention was not immediately successful were still included for analysis of clinical outcomes.

AFS is the time to major (above ankle) amputation or to death from any case whichever occurs first. OS is the time to death from any cause. LS is absence of major limb amputation FF-R is the absence of an attempt at further revascularisation of the index limb or of intervention relating to complications of the primary procedure. Minor amputations (distal to the ankle) were not considered a re-intervention as they are were considered more likely to be a consequence of the severity of the presenting clinical condition than the success of EVT. FF-MALE is the absence of any attempt at a further revascularisation, or a major amputation, of the index limb. MALE survival (MALE-S) is survival without MALE. LBP is a composite end-point based on factors; namely, radiological loss of patency, re-intervention or significant drop in ABPI (>0.15). We were unable to calculate LBP as, in the UK, routine post-intervention imaging and haemodynamic surveillance of CLTI patients undergoing EVT is not standard of care. We therefore report 12-month FF-R and FF-MALE instead. Pre-EVT digital subtraction angiograms (DSA) were GLASS assessed according to GVG instructions. The TAP was agreed by two assessors, LM and MP, and differences were settled with discussion; in those undergoing IP intervention the TAP was defined as the tibial vessel that underwent intervention. FP and IP segments were graded independently along with degree of calcification and combined to provide a GLASS stage for the overall limb. The pedal modifier was not used as foot views were not available for all patients. All patients had undergone evaluation, and where necessary endovascular and/or surgical correction of inflow disease prior to the index infra-inguinal EVT. Ethical committee approval was not required due to the retrospective design of this study, the study was registered with the institutional audit department. Differences in baseline patient characteristics between GLASS stages of disease were compared using t-test, χ^2-squared, Fisher's Exact test and Wilcoxon Rank Sum tests according to distribution

of data, Hazard ratios were used to detect statistically important differences in clinical outcomes using 95% confidence intervals. Statistical analysis was performed using SPSS v 24.

RESULTS

Baseline patient characteristics were similar between different GLASS grades and stages (**Table 3.6.1**). Increasing GLASS stage was associated with increasing age and those with FP grade 1 had significantly higher baseline creatinine. GLASS grades and stages and characteristics EVT are shown in **Tables 3.6.2 and 3.6.3**. There was no significant difference between the EVT performed and GLASS stage. There was a significant difference in the length of the index admission between GLASS stages (8.4 vs 12.6 vs 8.2 days, p=0.038) but total days in hospital was not different out to 12 months (29.0 vs 23.4 vs 23.1 days, p=0.516). ITS decreased significantly with increasing GLASS stage (I - 97.5% vs. II- 91.5% vs III - 84.0%, p=0.029) and were concordant with those set out as expected in the GVG.

Table 3.6.1 *Baseline demographics of patients by Global Limb Anatomic Staging System (GLASS) Stage*

	G1	G2	G3	Total	P value
Number	40 (12.9%)	82 (26.5%)	187 (60.5%)	309	
Male sex	22 (55%)	38 (46.3%)	90 (48.1%)	150 (48.5%)	0.657
Limb (Left)	21 (52.5%)	48 (58.5%)	105 (56.1%)	174 (56.3%)	0.817
Age (Years)	72.2	75.9	78.0	76.7	**0.006**

Rest Pain	9	19	62	90	0.111
Tissue Loss	27	52	92	171	
Both	4	11	33	48	
Stent	3	1	20	24	0.028
ITS	39 (97.5%)	75 (91.5%)	157 (84.0%)	271 (87.7%)	**0.029**
Index IP hospital days	8.4	12.6	8.2	9.4	**0.038**
12-month hospital days	29.0	23.4	23.1	23.9	0.516
Never Smoked	1	9	20	30	0.063
Ex-smoker	6	6	38	50	
Current Smoker	7	16	21	44	
Unknown	26	51	108	185	
DM	21	33	74	128 (41.4%)	0.311
CHF	4	9	11	24	0.295
HTN	26	53	133	212 (68.6%)	0.499
CAD	9	22	51	82 (26.5%)	0.823
COPD	5	12	18	35 (11.3%)	0.476
Creatinine (mmol/L)	128.6	126.1	97.6	109.2	**0.034**
Statin	24	50	123	197 (63.8%)	0.428
Antiplatelet	21	37	99	157 (50.1%)	0.272
Anticoagulation	10	22	52	84 (27.2%)	0.459
ACE	14	27	63	104 (33.7%)	0.466
B-Blocker	11	18	48	77 (24.9%)	0.428

CAD – Coronary Artery Disease

CHF – Congestive Heart Failure

COPD – Chronic Obstructive Pulmonary Disease

DM – Diabetes Mellitus

G1 – GLASS Stage 1

G2 - GLASS Stage 2

G3 - GLASS Stage 3.

HTN – Hypertension

Table 3.6.2 *Distribution of FP Grade and IP grade and numbers per Global Limb Anatomic Staging System (GLASS) Stage*

	FP 0	FP 1	FP 2	FP 3	FP 4
IP 0	0	6	20	45	95
IP 1	3	4	3	2	10
IP 2	7	2	9	9	19
IP 3	5	3	4	4	12
IP 4	6	2	4	8	27

GLASS Stage 1

GLASS Stage 2

GLASS Stage 3

FP – Femoro-popliteal grade

IP – Infra-popliteal grade

Table 3.6.3 *Distribution of arterial segments treated by Global Limb Anatomic Staging System (GLASS) Stage*

Arteries Treated	G1	G2	G3	Total
SFA	23	38	60	**121**
POP	0	9	32	**41**
SFA+POP	3	12	33	**48**
SFA+POP+Crural	3	6	19	**28**
SFA+Crural	2	3	9	**14**
POP+Crural	1	5	25	**31**
Crural	8	9	9	**26**
Total	**40**	**82**	**187**	**309**

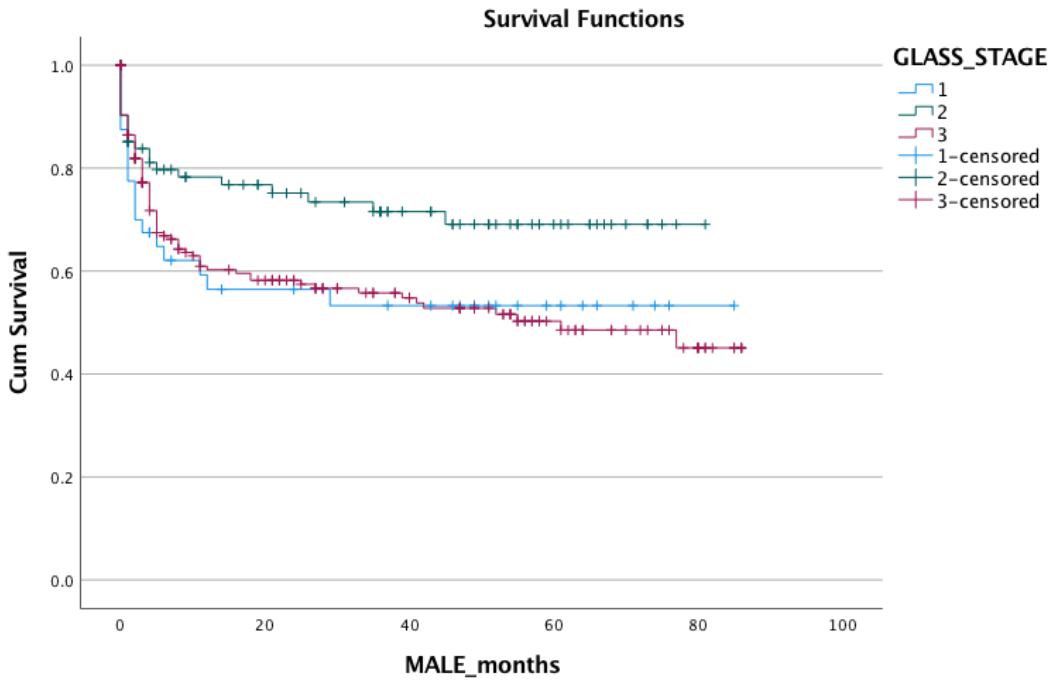
SFA – Superficial Femoral Artery

POP – Popliteal Artery

Crural – Anterior Tibial or Tibio-peroneal Trunk or Posterior Tibial or Peroneal

There was no significant difference between GLASS stage and 12-month FF-R (73%, 89% and 72%, p=0.419) or FF-MALE (59%, 78% and 61%, p=0.566). There was no significant relationship between GLASS stage and long-term AFS (38.6% vs 30.2% vs 36.9% p=0.710), OS (45.5% vs 28.8% vs 40.8% p=0.695) LS (73.7% vs 84.9% vs 74.7% p=0.771), FF-MALE (53.3% vs 69.1% vs 48.6% p=0.376), FF-R (68.6% vs 77.9% vs 55.4% p=0.172), or MALE-S (29.2% vs 16.4% vs 20.5% p=0.342) (**Figure 3.6.1)**.

Figure 3.6.1 *Major Adverse Limb Events (MALE) by Global Anatomic Staging System (GLASS) stage*

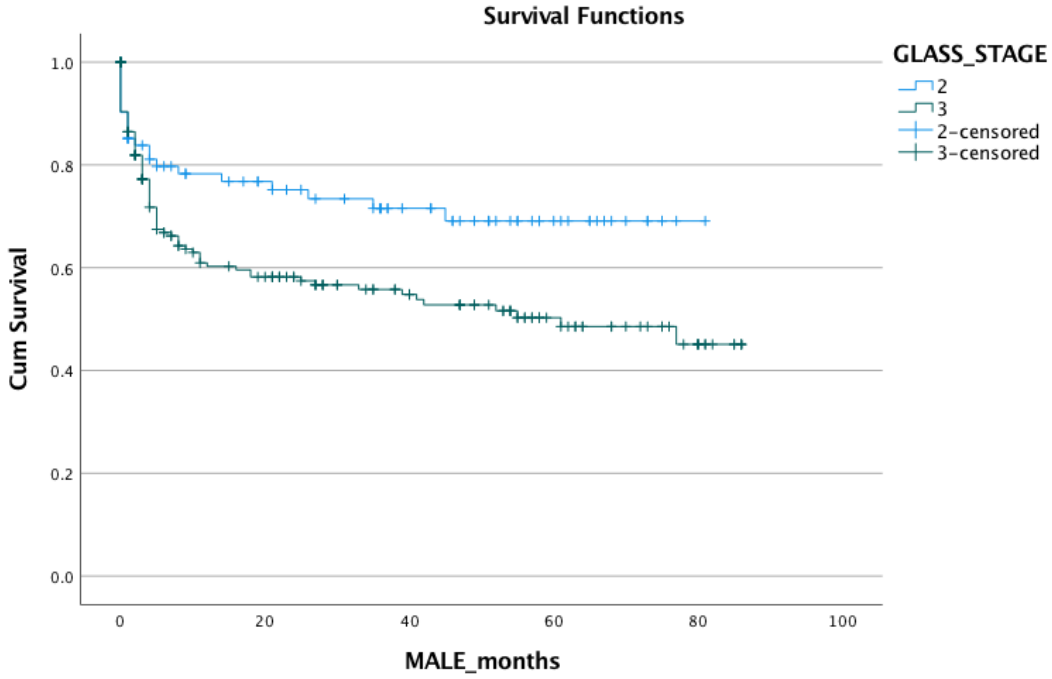


*numbers at risk

GLASS	12 M	24 M	36 M	48 M	60 M	72 M
1	20	18	17	13	7	3
2	52	44	34	25	14	6
3	89	75	60	48	29	18

However, 12-month (HR 1.83, 95% CI 1.07 - 3.12, p=0.026) and 24-month (HR 1.71, 95% CI 1.03 – 2.84, p=0.039) FF-MALE, and 12-month FF-R (HR 2.31, 95% CI 1.13-4.71, p=0.022) were significantly worse in limbs with GLASS stage III disease (**Figures 3.6.2 and 3.6.3)**.

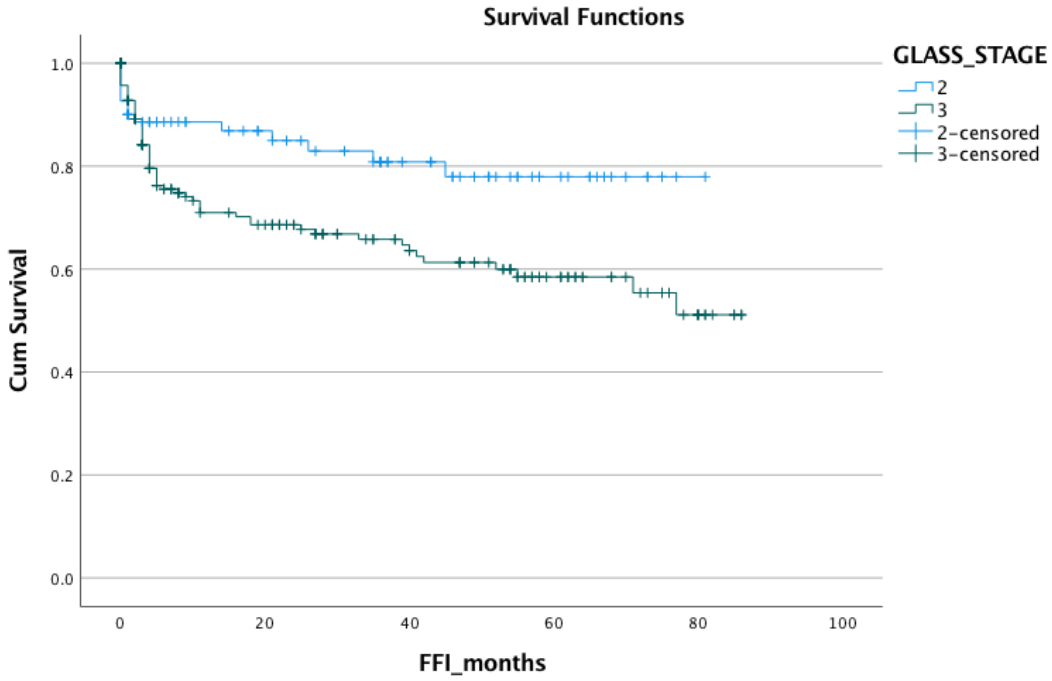
Figure 3.6.2 *A comparison of Major Adverse Limb Events (MALE) between Global Anatomic Staging System (GLASS) stage 2 and 3 disease*



*numbers at risk

GLASS	12 M	24 M	36 M	48 M	60 M	72 M
2	52	44	34	25	14	6
3	89	75	60	48	29	18

Figure 3.6.3 *A comparison of Freedom from Re-intervention (FFI) between Global Anatomic Staging System (GLASS) stage 2 and 3 disease*



*numbers at risk

GLASS	12 M	24 M	36 M	48 M	60 M	72 M
2	51	43	33	24	14	6
3	91	77	62	49	30	17

Out to 72 months follow up AFS (HR 0.95, 95% CI 0.67 – 1.35, p=0.780), OS (HR 0.76, 95% CI 0.55 – 1.06, p=0.107), LS (HR 1.57, 95% CI 0.78 – 3.16, p=0.207) and MALE-S (HR 1.16, 95% CI 0.86 – 1.55, p=0.332) were not significantly different between GLASS stage II and III disease. However, FF-MALE (HR 1.76, 95% CI 1.10 – 2.81, p=0.019) FF-R (HR 2.00, 95% CI 1.11 – 3.57, p=0.020) remained significantly worse for GLASS stage III disease in the long term.

There was no significant relationship between FP grade and 12-month FF-R and FF-MALE, or long term AFS (p=0.610), OS (p=0.180), LS (p=0.528), FF-R (p=0.229), FF-

MALE (p=0.834) and MALE-S(p=0.923). There was no significant relationship between IP grade, 12-month FF-R and FF-MALE, or long-term AFS (p=0.061), OS (p=0.570), LS (p=0.214), FF-R (p=0.980), FF-MALE (p=0.311) and MALE-S (p=0.122) (**Appendix 1)**. Using FF-MALE as a surrogate for LBP, observed outcomes are broadly similar to those set out as expected in the GVG (stage II 78% vs. 50-70%; stage III 61% vs. <50%).

DISCUSSION

The GVG recommends a PLAN (Patient risk, Limb severity, and ANatomic) approach to CLTI management. This emphasises the importance of considering patient fitness and limb threat (using WIfI(159)) alongside the anatomic disease severity when embarking upon shared decision making regarding infra-inguinal revascularisation(29, 195, 196). Regarding anatomy, GVG proposes GLASS as a method of predicting ITS and 12-month LBP in patients being considered for EVT. In our study, we found ITS significantly decreases with increasing GLASS stage, although ITS was somewhat better than that set out in GVG(197). Regarding FF-MALE and FF-R, GLASS stage III limbs had significantly worse outcomes than GLASS II limbs at 12, 24 and 72 months. Surprisingly, GLASS I limbs had outcomes similar to those with GLASS III disease. However, there were relatively few GLASS I limbs and we did not have WIfI data. So, unexpectedly poor outcomes in these limbs may be explained by limb threat due to wounds and/or infection rather than ischaemia. The pedal modifier was not calculated in this cohort, owing to inconsistency in the availability and quality of the angiograms, it is conceivable that pedal disease is the main contributor in GLASS I patients suffering with CLTI(198). Although GLASS was proposed as a means of predicting

12-month LBP, for reasons discussed, we substituted 12-month FF-MALE and FF-R. However, these end-points are mainly dependent on symptom recurrence and may miss patients with asymptomatic, or mildly symptomatic, treatment failures that would be captured by LBP based on haemodynamic testing and surveillance imaging. Prior to GLASS, TASC II was the most used tool for reporting on the disease severity. However, despite some correlation between limb-based outcomes and TASC II it has not been adopted into everyday practise(158, 199, 200). GVG authors hope GLASS based on grading and staging the EVT TAP will represent a significant advance and be more widely used. However, the authors recognise that without further validation and probably further refinement, GLASS cannot currently be used independently to assess the appropriateness of EVT for individual patients.

This studies limitations include its retrospective single centre design, no WIfI score, the inability to calculate the pedal modifier and the inability to specifically calculate limb based patency. Nevertheless, the authors have provided alternative data where possible to inform the reader of the degree of limb threat and success of endovascular therapy.

CONCLUSION

In summary, our study suggests that GLASS, when considered alongside patient fitness and limb threat, is likely to help predict ITS and 12-month limb-based outcomes in CLTI patients being considered for EVT. However, further refinement, particularly with respect to stage I disease in the context of different WIfI scores is probably required. To that end, we are prospectively gathering GLASS and WIfI data within the UK BASIL-2 and BASIL-3 trials which are expected to report in 2022 and 2023 respectively.

4 DISCUSSION

BASIL-1 was designed to investigate a difference in the primary outcome (AFS) between a PBA or an OSB revascularisation strategy first for CLTI, they found there to be a sustained difference in OS after two years in favour of OSB. Analysis of the BASIL-1 data (that concerned patients with FP disease) categorically demonstrated better outcomes in terms of FF-R and FF-MALE in patients undergoing OSB rather than PBA. Although the OS analysis was not superior for OSB there was a trend to better outcomes on the Kaplan-Meier curves. This was in-keeping with the main trial findings (BASIL-1 did not originally report FF-MALE), which concluded if patients were at low to medium risk and likely to survive more than two years, they should undergo OSB for revascularisation of CLTI. Add this to the findings that those patients who underwent SB after failed PBA faired far worse than those with primary OSB it is surprising to see that the mainstay of revascularisation for patients with CLTI is now endovascular i.e., despite the only level 1 evidence that we have recommending OSB as the primary revascularisation method for CLTI the specialty of vascular surgery has still followed a non-evidence-based strategy for revascularisation of CLTI – endovascular first.

The results presented in this thesis would indicate that outcomes for contemporary treatment of CLTI (particularly in those treated with endovascular revascularisation) are far worse than those observed in BASIL-1. AFS in the CS was far worse than that observed in BASIL-1, however the main contributor to that was worse OS rather than worse LS. Interestingly the same trend was seen in those patients undergoing OSB, with no significant difference in AFS between those patients treated with endovascular

or open revascularisation in the CS. It may be that these patients have a higher degree of frailty than those enrolled into BASIL-1, which is known to account for worse outcomes in this group of patients (especially in OS). To investigate whether these outcomes are generalisable, or unique to this centre only, further studies to compare this series with one or more local/national centre series (with risk adjustments) would provide helpful insight into the accuracy of those outcomes observed in the CS. To provide the most robust comparator it would be helpful to choose centres who adhere to the recommendations provided by BASIL-1 (if fit bypass first) and those who opt for endovascular first (like our CS) representing both strategies equally.

The results presented here are multifactorial, confounded by many systematic factors as well as selection bias and cannot only be attributed to endovascular versus OSB revascularisation. Maybe the results achieved in BASIL-1 were exceptional? Given the conditions provided within an RCT and the focus on care that is often seen when recruited into a trial, it maybe that those enrolled in BASIL-1 received far better care than what would 'normally' be delivered(201, 202). It must be said that BASIL-1 did not prescribe a mandatory clinical follow up period (determined by the responsible clinicians) or a deviation in post-operative clinical surveillance (survey as they would normally) for recruiting centres. Neither did BASIL-1 prescribe expectations for wound care, or thresholds for re-intervention. In truth the only deviation from standard care for the randomising institution was the type of revascularisation. As sometimes is seen with trials, only the 'best' patients are enrolled – meaning they are the most likely to succeed and survive. A small proportion of patients screened for BASIL-1 were enrolled into the trial (approx. 15%), this may explain some of the survival differences between BASIL-1 and the CS cohort (all comers). In terms of the patient cohort, they were older than BASIL-1 and therefore worse survival is to be expected. Contrary to

this was the better levels of BMT – this however may represent more treated co-morbidities (and more medical care prior to requiring revascularisation), and therefore by extension more frailty. BMT is instituted as secondary prevention of MACE, not for limb-based outcomes – we did not observe better limb-based outcomes in the CS versus those treated in BASIL-1.

The BEST-CLI trial has recently reported its results and is now the reference study for vascular surgeons to inform decisions regarding revascularization in patients with CLTI. BEST-CLI is an exceptional effort, the trialist must be commended on their ability to recruit nearly 2000 patients into a surgical RCT in an area where equipoise has significantly hindered recruitment. The trial design is methodologically robust, and their composite outcome would seem to be the most descriptive contemporary measure of successful revascularisation, it is disappointing that they did not report AFS to allow direct comparison with the previously published literature. Although under-recruited the power of the findings remained unchanged due to larger number of events than predicted within the endovascular arm. Minimum 2 year follow up (as planned) was achieved with extra funding (societal and industry) to ensure the trial was able to report useful mid-term clinical outcomes.

In terms of included patients, females are under-represented compared to expected for the CLTI population, the ethnic distribution however is consistent to that reported previously (203). Data completeness was acceptable, however 15% did not have a WIfI score and approximately 15% were missing data for stratification on randomisation (compensated for statistically). Best medical therapy rates were superior to those seen in BASIL-1, however, 35% of patients were still smoking, only 70% were taking statin therapy and more (70%) were diabetic. The average age of

the patients within BEST-CLI was 67 years, compared to 72 in BASIL-1 and 75 in the CS.

Few major adverse events were identified to question safety of the trial, and adverse outcomes in the first 30 days post intervention were low for both interventions in both cohorts. In most vascular surgery trials, the open surgery arm often has a noticeably higher death rate in the first 30 days post intervention which then normalises over time(20, 204-206), this was not observed in BEST-CLI with 30-day death similar between both treatment strategies (Cohort 1 OSB 19 vs BET 16). Approximately 20% of recruited patients had rest pain only (Rutherford 4) with the majority suffering with additional tissue loss (Rutherford 5,6), which is consistent with the proportions expected. Although the mean ABPI (0.58) is higher than expected, this may be explained by the high proportion of diabetes in the cohort, as mean toe pressure was 36mmHg – which is more consistent with CLTI due to ischaemia.

In terms of clinical outcomes, the results achieved are comparable to those reported in BASIL-1 20 years ago, apart from freedom from re-intervention, which was approximately 15% superior in both arms of the trial compared to BASIL-1. In terms of OSB, OS (BEST-CLI 67% vs 69% BASIL-1), LS (89.7% vs 85%) were comparable. Similar results were observed for BET, OS (62.4% vs 63%) and LS (85.2% vs 84%). Both trials therefore had significantly better outcomes compared with CS (OS OSB 29% vs BET 34% and LS 73% vs 76%). With the headline result for the primary outcome (MALE-S) demonstrating OSB with GSV was superior to EVT (42.6% in OSB vs 57.4% for EVT (HR 0.68; 95%CI 0.59-0.79, $p<0.001$). The majority of this difference was driven by re-intervention rather than OS or MLLA.

Much of the literature and clinician opinion would support that in older patients (>80 years) people with renal impairment, female sex, recurrent surgery and less severe

disease (rest pain – Rutherford 4) BET would be the 'better' treatment option, Cox-regression analysis performed in BEST-CLI would suggest that these groups trended to better outcomes after OSB in Cohort 1 with no predominance for better outcomes after BET in Cohort 2.

We must therefore conclude that there are now two RCT's, 20 years apart, that demonstrate OSB provides better quality revascularisation (in terms of important clinical outcomes) compared to EVT for patients who could be treated with both techniques.

Are the results of BEST-CLI relevant to patients in the UK? In terms of patient demographics, BEST-CLI recruited multi-morbid patients receiving best medical therapy who had documented severe ischaemia (in terms of haemodynamic measurements) as well as significant tissue loss in the limb (~80%), which is similar to those included in BASIL-1 and the CS reported in this thesis. BASIL-2 and 3 will inform whether there has been a diversion in the types of patients developing or being treated for CLTI within the UK. In terms of interventions, the OSB philosophy (Single segment GSV as the preferred conduit) is the same as that which is practised here in the UK. Where there may be significant difference is the method of endovascular intervention. As described throughout this thesis, within the UK the mainstay of BET is PBA +/- bailout BMS, within BEST-CLI, far more 'modern' interventions were deployed in high frequency. Within the trial, only 55.4% underwent PBA alone, with 37.2% of patients having stents deployed. Significant numbers of patients underwent atherectomy (~13.6%) or stent grafting (~ 3.4%), in addition, 35.4% received treatment with a drug eluting device (DCB 22.7%, DES 15.7%). As well as the type of devices used, >70% of the endovascular interventions were solely performed by vascular surgeons. Therefore BEST-CLI is likely to represent the endovascular treatment to be

expected in the UK in the future rather than currently, arguments need to be made as to whether this evolution is beneficial for patients and cost effective.

The GVG recommend a PLAN approach to patients with CLTI. This thesis highlights that very few clinicians were practising in this way prior to the release of the GVG. Very little effort is made to stratify the patient risk currently, decisions in terms of risk are made on a review of the notes and end of bed impression – there is no formal scoring or documentation of risk. It maybe that with an endovascular first strategy, patient risk is low priority as very few suffer immediate systemic complications from endovascular revascularisation, meaning very few are denied intervention. Limb assessment is also non-structured. Many clinicians believe 'high risk' wounds are identified with good clinical assessment, and formal scoring is superfluous. Patients are now managed by many consultants though their journey, formal assessment allows for detailed grading of wound severity, aiding comparison between different observers and decisions regarding clinical improvement/decline. The SVS WIfI is the preferred tool to systematically score the degree of ischaemia, infection and size of the wound and has immense potential not only to identify those patients who are 'high risk' but also monitor effectiveness of treatment and identify those patients who require more intervention during follow-up by means of worsening scores due to worsening ischaemia or recurrent wound infection.

Finally, anatomy of the disease is considered when contemplating intervention/revascularisation. Previous systems (TASCI/II) were never adopted into routine clinical practise and therefore clinicians have developed their own thresholds for what they determine to be a good EVT or OSB candidate. It is true (as observed in this thesis) that ITS, treating technically complicated lesions (full length FP disease etc), have improved since BASIL-1. But little is documented as to the prolonged

technical success of these interventions and whether they indeed translate into clinical success. The GLASS score is designed to overcome this problem, it is simple to calculate and gives thresholds of where you can expect robust enduring technical success (S1) and where you are likely to fail (S3). If adopted widely it could be used in MDT discussions to actively stratify lesions and inform decisions on likely success of EVT.

As well as the lack of structured pre-intervention assessment, post intervention care and surveillance are often not at the standard expected for such complex critical patients. The GVG and NICE CG147 recommend patients are enrolled in clinical surveillance post discharge this can be with or without ultrasound surveillance of the treated arterial segment/graft. HEFT did not have a standardised surveillance programme for patients with CLTI. Most patients underwent intervention and clinical review 6-8 weeks post intervention. At which point if they were progressing positively, they were discharged with instructions to return if they experienced deterioration. Those who were not progressing well would go on for further investigation and intervention. We know that limb complications (in those revascularized) can occur at any point however are most likely in the first 12 months out to 24 months. Often there are subcritical stenosis that do not become apparent until it is too late, or patients suffer at home in denial about their symptoms for fear of further intervention or amputation and present too late for salvage.

As well as clinical practise deficiencies, many of the problems faced are created by organisational re-structuring. Vascular surgery services in the UK are now (in the majority) centralised to large arterial hubs after the drive to improve outcomes for patients undergoing aortic aneurysm surgery and carotid surgery, where hospital volume has been shown to improve surgical outcomes(207). The organisational re-

structure has led to less vascular surgical team coverage of the 'spoke' (smaller) hospitals, fewer available 'spoke' clinics, less local diagnostic capacity (vascular sonographers) and no local arterial intervention. Hubs have struggled to increase inpatient and theatre capacity to deal with increased central workload meaning difficulties in accessing vascular services in timely fashion. Because of the increased focus on abdominal aortic aneurysm (AAA) and carotid endarterectomy outcomes, patients suffering with CLTI have been given lower priority, delaying times to assessment, investigation and treatment. The constraints on theatre space may be pushing clinicians to treat more patients with EVT. More patients can be treated on each intervention radiology list (local anaesthesia, fewer technical steps in each procedure), meaning higher patient throughput, therefore intervention can be offered more quickly – even if it is the substandard intervention for certain patients.

The data presented here are a subgroup from a multicentre RCT (BASIL-1) along with a retrospective cohort of patients from one university hospital trust (CS). Those that have peer reviewed the chapters regarding the subgroup analyses within the BASIL-1 trial have questioned their appropriateness as the trial was not designed to answer those specific questions. We argued that BASIL-1 (at the time of publication) was the least biased data available to address these questions, and the analysis were of interest to the vascular community and indeed increased (in a small way) the evidence base for treatment of patients with femoro-popliteal induced CLTI. It can be argued that comparison of the two groups (BASIL-1 vs CS) is flawed as both populations are different as well the selection bias within the CS. The intention here was to use the BASIL group as a 'control' with the CS as the intervention group (due to the strict preference for an endovascular first strategy for FP-CLTI) and within this context these analyses are appropriate – as well as there being little demographic difference

between the cohorts (except age). Finally, the poor staging of limbs in both cohorts makes understanding the degree of limb threat difficult, particularly in those patients in the CS with GLASS stage 1 disease. This data would have been extremely useful to fully understand some of the treatment effects in patients with less severe anatomical disease (GLASS stage 1). This thesis provides a large number of clinical outcomes; however, this does not allow us to judge the effect on quality of life, which is often the most important outcome for patients. Neither was it possible to provide accurate data on important factors such as relief of rest pain or wound healing which are also important measures of successful treatment. Future studies should include patient related outcome measures (PROMs) and patient experience measures (PREMs).

What needs to be done to improve the quality of care for patients with CLTI? CLTI needs to be recognised as a health condition that requires prioritisation by patients, public health and primary/secondary care. Worryingly high amputation rates coupled with regional and ethnic variation has brought this issue to the attention of the all-party parliamentary group on vascular and venous diseases, who are now concentrating government efforts to improve amputation rates for diabetics and non-diabetics across the whole country(208). Government policy needs to encourage (which can be aided by secondary care) early recognition of PAD by General Practitioners with initiation of risk factor modification (antiplatelet, statin, blood pressure and diabetes control) to prevent progression to CLTI as well as MACE. The Vascular Society of Great Britain and Ireland have published their peripheral arterial disease quality improvement framework (VSGBI PAD-QIF)(209) in an attempt to raise the profile of peripheral arterial disease (mainly within secondary care settings), and emphasise the importance of timely investigation and treatment in achieving good outcomes. It

recommends that inpatients diagnosed with CLTI receive investigation and treatment within 5 days and outpatients within 14 days. It recognises that these are challenging targets for most, if not all, vascular units, to meet them will require significant service restructuring. This will require streamlined pathways for expedient admission/transfer to arterial hubs from spoke hospitals, as well as quick access to cross sectional imaging and finally capacity within the intervention radiology suite or vascular theatre for early revascularisation. Given the current stresses on the NHS each will be challenging with all users demanding better access to services within the confines of current resourcing.

The framework recommends establishing a dedicated limb salvage service, similar to those established in Leicester (VaLS clinic)(210) and Greater Manchester (MARS)(211), the VaLS clinic reporting a 50% RRR in major lower limb amputation (out to 12 months). Structured decision making within these 'new' pathways is essential to standardising assessment and care. It is becoming clear that the GVG PLAN approach should be used for all patients attending with suspected CLTI. Patients risk should be estimated at baseline, none are in routine use currently and are not accurate enough to entirely lead clinical decision making, however, stratification of risk is useful when communicating intervention options to patients and will allow better refinement with audit of outcomes. Units should agree a risk estimation tool and use this routinely for all patients. Limb risk estimation should be formalised with WIfI scoring on presentation and along the patient journey. Establishing a target artery pathway (TAP) to achieve inline pulsatile flow to the foot should be the aim of revascularisation, GLASS scoring should be used to estimate the likely success of endovascular intervention for every patient. In combination, these elements should allow for EBR and better outcomes for patients. An example here

would be a patient deemed high physiological risk with intermediate WIfI score (2,3) and a GLASS stage of 2, endovascular intervention would be the better choice of revascularisation in this patient. Conversely, a patient deemed low physiological risk with an intermediate WIfI score (2,3) and GLASS stage 3 should be offered OSB as the preferred revascularisation option. The aim should be to follow the recommendations of the BASIL-1 trial as well as the new BEST-CLI trial.

Post intervention follow up is heterogenous across the country, with varying pathways (if any at all), the GVG and NICE recommend clinical surveillance post revascularisation for 12-24 months with or without ultrasound. As a minimum, centres who are involved in limb salvage should routinely clinically survey their patients (either by clinical examination in the outpatient department or ABPI/TBPI/Doppler at standardised regular intervals). Those patients with neuropathy or altered foot architecture should be regularly assessed by podiatry to ensure footwear and offloading is optimised to prevent recurrent ulceration.

What research should be conducted in the future to better inform this area? When BASIL 2 & 3 report, and the individual patient data meta-analysis is conducted, there should be a good understanding as to the hierarchy of OSB with vein, OSB with synthetic conduit, PBA with or without stenting, Drug eluting devices (DES/DCB) in the Fem-pop and infra-pop arterial tree.

The GVG recommendation that I have endorsed in this thesis of using the PLAN approach to patients with CLTI is very likely to move things forward – with the hope this will improve outcomes. This approach to patients needs validation in many health care settings of varying populations, however, should be achievable for research collaboratives and large institutions seeing many patients per year with CLTI.

More evidence is needed on the benefits of early risk factor modification on preventing progression to CLTI and indeed, if progression, better outcomes. This could be achieved with a study investigating the benefits of screening for peripheral arterial disease. Vascular surgery in the UK has already established the national AAA screening programme (NAAASP)(212), incidence of AAA is declining(213) threatening the cost-effectiveness of continuing to screen men for AAA, this programme could be adapted to screen for PAD as well as AAA with very little additional cost if doing so was found to be beneficial and cost effective.

Pedal disease is now a much larger problem due to the increasing rates of diabetes; no formal study has been conducted to understand its exact effect on success of revascularisation (although thought to be negative). It may be that revascularisation in patients who have had formal pedal assessment (and operative strategy adjusted to compensate for any disease identified) may be more successful than those where this has not been done, especially in patients who have been revascularized based n MRA/CTA. If patients do have pedal disease, that does not preclude revascularisation, could the addition of biological treatment to improve angiogenesis be beneficial to increase the capillary bed for perfusion? There have been some trials in patients with no-option CLTI(214-219), but could there be an additive effect with successful revascularisation?

Optimal antiplatelet/anticoagulation therapy needs urgent attention as again this area of therapy is currently heterogenous and largely non-evidence based. The number of patients in such a trial would have to be very high (many thousands) and would likely have to be industry sponsored (cost), however a standardised approach would be helpful for inpatient teams, patients and our colleagues in general practice.

Finally, as well as ischaemia and infection being important in wound healing, nutrition (specifically vitamins and trace metals) have an important role in facilitating wound healing. Currently we have a poor understanding of the exact nutritional state of our patients. This needs to be established and then investigate whether improving these deficiencies improves wound healing.

Answering these questions requires funded trials and engagement from the vascular society. An area that has been particularly problematic in large, national trials of patients with CLTI (BASIL 1,2,3 and BEST-CLI) has been clinician equipoise. Decision making regarding which intervention is best is guided by experience, confidence in self and others and group mentality. Vascular surgeons believe they know which is the best treatment for certain disease patterns and are uneasy about potentially exposing patients to an inferior treatment (poor technical outcomes are often non salvageable, which lead to amputation or death). As well as this being the case on an individual basis, it is often re-enforced by the MDT process (especially if a group of clinicians have been working closely together for some-time), making changing opinion (even if the data would suggest there is equipoise) very difficult. BASIL 2 and BEST-CLI had to stop recruitment due to such slow rates of enrolment it was not cost effective to continue. Unless we find a way of establishing equipoise in decision makers minds it is likely that intervention trials in vascular surgery will continue to suffer the same problems with recruitment which may make it more difficult to gain successful funding from NIHR.

As a vascular surgeon that has been appointed to a consultant role in the last year, in an area with large deprivation, smoking, obesity and diabetes I see the massive challenge of limb salvage on a daily basis. Currently there is a difficult struggle to achieve limb salvage in these patients, and our amputation to revascularisation ratio

is >1 at this present time! Many of the adaptions I have discussed in this thesis need to be adapted within the service I am currently employed. Competition for space, resource and favour among the executive is fierce, coupled with the organisations monocular focus on improving flow through the emergency department, implementing meaningful change is difficult (especially if it requires funding). In the short to medium term as the population continues to age, and the prevalence of diabetes increases, the number of patients with CLTI is likely to increase. A larger proportion of our effort and resource will need to be directed at this patient group to manage the demand. Ultimately, the incidence of arterial disease is declining, one can foresee a time where our focus will be on treating remaining arterial disease medically and we practice more as vascular specialist rather than primarily surgeons.

5 CONCLUSION

We have observed a trend towards an endovascular first approach to revascularising patients with femoro-popliteal induced CLTI. Better clinical outcomes were observed in the subgroup analysis of the BASIL-1 trial, and indeed those requiring salvage with SB fared worse than those who underwent primary OSB. Employing an endovascular first resvascularisation strategy has led to worse clinical outcomes for those patients undergoing OSB and EVT in the CS compared to BASIL-1. In the light of the publication of the Global Vascular Guideline and the BEST-CLI trial, vascular surgeons need to re-think their approach to patients with CLTI as contemporary outcomes do not support the deviation from the BASIL-1 recommendations, in acceptable risk patients suffering with CLTI OSB first should still be the revascularisation preference.

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Appendix 1

Supplemental tables for chapter 3.6.

Table 1. *Short-term survival estimates by FP grade.*

12 months	FP 0	FP 1	FP 2	FP 3	FP 4
FF-R	85%	67%	83%	83%	72%
FF-MALE	67%	58%	66%	75%	61%

Table 2. *Long-term survival estimates by FP grade.*

72 months	FP 0	FP 1	FP 2	FP 3	FP 4	P Value
AFS	91%	33%	36%	28%	29%	0.610
LS	68%	74%	65%	81%	71%	0.528
FF-R	69%	67%	74%	75%	50%	0.229
FF-MALE	54%	51%	57%	69%	45%	0.834
OS	21%	46%	36%	31%	43%	0.180
MALE-S	7%	15%	19%	21%	23%	0.923

Table 3. *Short-term survival estimates by IP grade.*

12 months	IP 0	IP 1	IP 2	IP 3	IP 4	P Value
FF-R	75%	90%	83%	84%	66%	0.888
FF-MALE	66%	79%	66%	71%	53%	0.269

Table 4. *Long-term survival estimates by IP grade.*

72 months	IP 0	IP 1	IP 2	IP 3	IP 4	P Value
AFS	29%	32%	15%	31%	23%	0.061
LS	77%	88%	52%	68%	66%	0.214
FF-R	51%	78%	75%	79%	50%	0.980
FF-MALE	48%	69%	60%	66%	40%	0.311
OS	38%	30%	42%	20%	40%	0.570
MALE-S	18%	21%	24%	7%	11%	0.122

Table 5. *72-month clinical outcomes by Glass stage 1,2 and 3*

	G1	G2	G3	P Value
AFS	39%	30%	37%	0.711
LS	76%	85%	75%	0.772
FF-R	69%	78%	55%	0.159
FF-MALE	53%	69%	49%	0.369
OS	46%	29%	41%	0.695
MALE-S	29%	16%	21%	0.337

Table 6. *72-month clinical outcomes by Glass stage 2 and 3*

	G2	G3	P Value
AFS	30%	37%	0.781
LS	85%	75%	0.189
FF-R	**78%**	**55%**	**0.013**
FF-MALE	**69%**	**49%**	**0.014**
OS	29%	41%	0.107
MALE-S	16%	21%	0.328

Appendix 2

Appendix 2 contains the published chapters as they appear in print (3.1-3.6).

Eur J Vasc Endovasc Surg (2019) 58, 52–59

A Comparison of Clinical Outcomes Following Femoropopliteal Bypass or Plain Balloon Angioplasty with Selective Bare Metal Stenting in the Bypass Versus Angioplasty in Severe Ischaemia of the Limb (BASIL) Trial

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WHAT THIS PAPER ADDS

This by-treatment-received analysis of data from the publicly funded Bypass Versus Angioplasty in Severe Ischaemia of the Limb (BASIL-1) randomised controlled trial (RCT) confirms the superiority of bypass over plain balloon angioplasty, with or without bare metal stenting, in patients with chronic limb threatening ischaemia who require femoropopliteal intervention. Although the interventions were carried between 1999 and 2003, there are no more recently acquired randomised data that contradict the findings presented here. BASIL-1 trial data therefore remain an important and relevant standard with which to compare outcomes in current vascular and endovascular practice and the results of ongoing, publicly funded, pragmatic RCTs, such as BASIL-2, BASIL-3, and BEST-CLI.

Objective: To compare outcomes in patients with chronic limb threatening ischaemia (CLTI) due to femoropopliteal (FP), with or without infrapopliteal (IP), disease who underwent FP (vein or synthetic) open surgical bypass (OSB), or plain balloon angioplasty (PBA), with or without bare metal stenting (BMS), in the Bypass versus Angioplasty in Severe Ischaemia of the Limb (BASIL-1) trial.

Methods: Data were extracted from BASIL-1 case record forms. Outcomes reported include immediate technical success, freedom from major adverse limb events (FF-MALE) and further re-intervention (FF-R), amputation free survival (AFS), overall survival (OS), and limb salvage (LS).

Results: Patients underwent primary OSB ($n = 128$; 89 vein, 39 synthetic) or primary PBA ($n = 183$; six had BMS). Mean follow up was 46.2 and 43.6 months respectively. Patients were well matched at baseline except that PBA ± BMS patients were significantly more likely to be current smokers. There was no difference in overall or IP (runoff) Bollinger angiogram scores between groups. Immediate technical success was significantly higher for OSB (98% vs. 81%; $p < .001$). OSB was associated with a longer mean index hospital admission ($p = .001$), but there was no difference in hospital days at 12 months. FF-MALE (hazard ratio [HR] 1.51; $p = .04$) and FF-R (HR 1.68; $p = .02$) but not AFS (HR 1.18; $p = .4$), OS (HR 1.14; $p = .5$), and LS (HR 1.09; $p = .8$) were significantly better after OSB.

Conclusion: Although AFS, OS, and LS were similar in the two groups, OSB was associated with significantly fewer MALE and re-interventions. So, while PBA ± BMS may be a less resource intensive (expensive) and morbid option in the short term, this appears unlikely to be the case in the longer term. Present data add further weight to the argument that, where possible, patients presenting with CLTI due to FP disease should be offered OSB as their primary revascularisation procedure.

Keywords: Chronic limb threatening ischaemia, Femoropopliteal bypass, Peripheral arterial disease, Plain balloon angioplasty
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INTRODUCTION

The Bypass versus Angioplasty for Severe Ischaemia of the Leg trial, now known as the BASIL-1 trial, remains the only published randomised controlled trial (RCT) to have compared an open surgical bypass (OSB) first, with a plain balloon angioplasty (PBA), with or without bare metal stenting (PBA ± BMS), first revascularisation strategy for chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease.[1,2] In BASIL-1, approximately 75% of patients had predominantly femoropopliteal (FP) disease and intervention, while in about 25% the disease and intervention were predominantly infrapopliteal (IP). A recently

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Table 1. Baseline characteristics in patients undergoing open surgical bypass and plain balloon angioplasty ± bare metal stent

	Surgical bypass (n = 128)	PBA ± BMS (n = 183)	p value
Conduit			
Vein	89 (70)	–	
Synthetic	39 (30)	–	
PBA ± BMS	–	183 (100)	
Men	78 (61)	94 (51)	.09
Right limbs	57 (45)	75 (41)	.50
Mean age ± SD, years	71.7 ± 8.0	73.1 ± 8.6	.20
Mean follow-up ± SD, months	46.2 ± 27.2	43.6 ± 24.7	.40
Indication			
Rest pain	52 (41)	69 (38)	.40
Tissue loss	14 (11)	14 (8)	
Both	62 (48)	100 (55)	
Mean creatinin ± SD, μmol/L	111.7 ± 79.4	107.7 ± 60.2	.60
Smoker			
Never	17 (13)	36 (20)	.04
Ex-smoker	65 (51)	67 (37)	
Current	46 (36)	80 (44)	
Diabetes mellitus	47 (37)	74 (40)	.50
Congestive heart failure	5 (4)	8 (4)	.80
Hypertension	77 (60)	108 (59)	.80
Coronary artery disease	35 (27)	50 (27)	1.00
Chronic obstructive airway disease	19 (15)	15 (8)	.06

Data are n (%) unless otherwise indicated. PBA = plain balloon angioplasty; BMS = bare metal stent; SD = standard deviation.

published BASIL-1 IP subgroup analysis showed that, when compared with PBA (no IP BMS were used), a vein bypass (VB) first strategy resulted in better overall survival (OS), amputation free survival (AFS), and quality of revascularisation (time to wound healing and relief of ischaemic rest pain).[3] Despite BASIL-1, the only currently available "level 1" evidence, showing better long-term clinical outcomes following OSB, there has nevertheless, been a non-evidence based trend towards offering primary endovascular intervention to patients with CLTI due to FP disease. The aim of this BASIL-1 subgroup analysis, therefore, is to compare outcomes in patients who underwent FP OSB (VB and synthetic [SynB]) or PBA ± BMS as their primary revascularisation procedure.

METHOD

BASIL-1 trial

BASIL-1 methods and ethical approvals have been published previously.[4] In brief, between August 1999 and June 2004, 452 patients with CLTI due to infra-inguinal disease were randomised to an OSB first or a PBA ± BMS first revascularisation strategy. Patients were eligible for trial inclusion if the responsible clinicians felt that they required early revascularisation and were in clinical equipoise between OSB and PBA ± BMS. Patients were followed up by six dedicated research nurses at one, three, six and 12 months post-randomisation and then annually until death or 1 July 2007. The primary end point was AFS and secondary end points included OS, limb salvage (LS), and requirement for re-intervention. BASIL-1 was a multicentre, pragmatic, clinical effectiveness RCT that allowed participating units to continue to use their preferred post-intervention surveillance programmes. However, the majority of the re-interventions were due to persisting or recurrent symptoms and signs of CLTI.

Inclusion criteria for FP subgroup analysis

In order to be included in the current subgroup analysis, BASIL-1 patients had to fulfil two criteria. Firstly, they had to have atherosclerotic FP disease causing CLTI and, secondly, they only underwent intervention to the FP segment (with no IP intervention). Baseline and clinical outcome data were extracted from the original prospectively gathered BASIL-1 case record forms.

Outcomes

In this BASIL-1 FP subgroup analysis, immediate technical success (as defined by the operating surgeon or interventionalist), mean length of index hospital admission, days spent in hospital out to 12 months from randomisation, freedom from major adverse limb events (FF-MALE) and re-intervention (FF-R), AFS, OS, and LS are reported. Major amputation was classified as amputation of the trial limb above the ankle. Minor amputation as a re-intervention is not included as this is regarded as being mainly determined by the condition of the foot at presentation and not by the type of primary revascularisation. MALE comprised any revascularisation attempt or major amputation of the trial limb during follow up. Post-procedural complications are reported as 30 day mortality, morbidity (complications and re-interventions), and major adverse cardiovascular event that comprises death, myocardial infarction, or cerebrovascular event. Unplanned interventions for post-operative complications, revascularisation (OSB or PBA ± BMS), or

Table 2. A comparison of Bollinger scores between open surgical bypass and plain balloon angioplasty ± bare metal stent groups

Arterial section	Surgical bypass (n = 128)	PBA ± BMS (n = 183)	p value
Profunda femoris	1.6 ± 2.6	2.1 ± 3.4	.20
Proximal superficial femoral	7.0 ± 5.9	7.0 ± 5.5	.90
Distal superficial femoral	10.3 ± 4.9	10.2 ± 5.0	.80
Proximal popliteal	6.9 ± 5.8	7.1 ± 5.7	.70
Distal popliteal	1.5 ± 2.5	2.7 ± 4.4	.007
Tibioperoneal trunk	2.5 ± 3.6	2.8 ± 4.3	.60
Proximal posterior tibial	6.8 ± 5.9	8.2 ± 6.6	.05
Distal posterior tibial	8.3 ± 6.6	9.3 ± 6.5	.10
Proximal peroneal	4.4 ± 4.8	4.6 ± 5.2	.70
Distal peroneal	5.8 ± 6.2	4.5 ± 5.6	.10
Proximal anterior tibial	6.0 ± 6.1	5.8 ± 5.7	.80
Distal anterior tibial	7.2 ± 6.8	6.7 ± 6.6	.60
Plantar	6.7 ± 4.0	6.5 ± 4.4	.80
Total	*70.7 ± 24.5*	*75.1 ± 27.3*	*.20*
Total infrapopliteal	*44.4 ± 22.4*	*46.6 ± 24.1*	*.40*

Data are mean Bollinger scores ± standard deviation. PBA = plain balloon angioplasty; BMS = bare metal stent.

major amputation were collated and reported under the term surgical re-interventions if they occurred within 30 days. No patients were lost to follow up for the primary end point or the other secondary end points reported here. Patients who partially withdrew had their clinical outcome data collected via UK centralised databases, now known as the Office of National Statistics (ONS) and hospital episode statistics data.

Statistics

Time to event analyses comparing all OSB (VB and SynB) with PBA ± BMS are presented over a seven year period using Kaplan—Meier plots and the log rank test for significance. Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals (CIs). Differences between the groups were compared using Student t, chi-square, and Wilcoxon rank sum tests according to distribution of data using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Demographics

There were 311 patients; 128 underwent primary OSB (89 VB, 39 SynB) and 183 had primary PBA ± BMS (six stents). Mean lengths of follow up were 46.2 months (range 0—91 months) and 43.6 months (range 0—93 months), respectively. Ipsilateral great saphenous vein was used for 83 (93%) VB; arm vein was used for 1 (1%) and composite vein (arm and leg vein spliced) for five (6%). Most VB were reversed (n = 63; 71%), with 23 (26%) being *in situ* and three (4%) non-reversed. The two groups were very similar in terms of baseline characteristics although PBA ± BMS patients were more likely to be current smokers, and there was a trend to more chronic obstructive pulmonary disease in OSB patients (Table 1).

Distribution of disease

There was no significant difference in the overall burden of disease between the two groups in terms of Bollinger angiographic scores (p = .2) (Table 2). IP disease severity was also statistically similar in the two groups (Bollinger score 44.4 vs. 46.6; p = .4) with the peroneal artery being the least diseased runoff vessel.

Short-term outcomes

Immediate technical success was highly significantly better for OSB (98% vs. 81%; p < .001). Although patients undergoing OSB had a longer median (interquartile range [IQR]) index hospital admission (16 days [IQR 10—27] vs. 8 days [IQR 2—19]; p = .001), by 12 months patients in both

Table 3. Morbidity and mortality (30 day) in patients undergoing open surgical bypass and plain balloon angioplasty ± bare metal stent

	Surgical bypass (n = 128)	PBA ± BMS (n = 183)	p value
Mortality (30 d)	7 (5)	6 (3)	.30
Morbidity and mortality (30 d)	58 (45)	59 (32)	.02
Myocardial infarction	5 (4)	5 (3)	.60
Transient ischaemic attack	0	2 (1)	.20
Cerebrovascular accident	1 (1)	3 (2)	.50
Haematoma (not operated)	7 (5)	8 (4)	.70
Haematoma (operated)	2 (2)	1 (1)	.40
Wound infection[a]	37 (29)	29 (16)	.006
Lower respiratory tract infection	4 (3)	5 (3)	.80
Urinary tract infection	2 (2)	3 (2)	1.0
False aneurysm (not operated)	1 (1)	0	.2
False aneurysm (operated)	0	0	–
Major amputation	3 (2)	9 (5)	.3
Surgical intervention (30 d)	3 (2)	13 (7)	.06
Major adverse cardiovascular event	10 (8)	10 (5)	.4

Data are n (%).
[a] Includes foot infection, as well as infection at the intervention site. PBA = plain balloon angioplasty; BMS = bare metal stent; d = days.

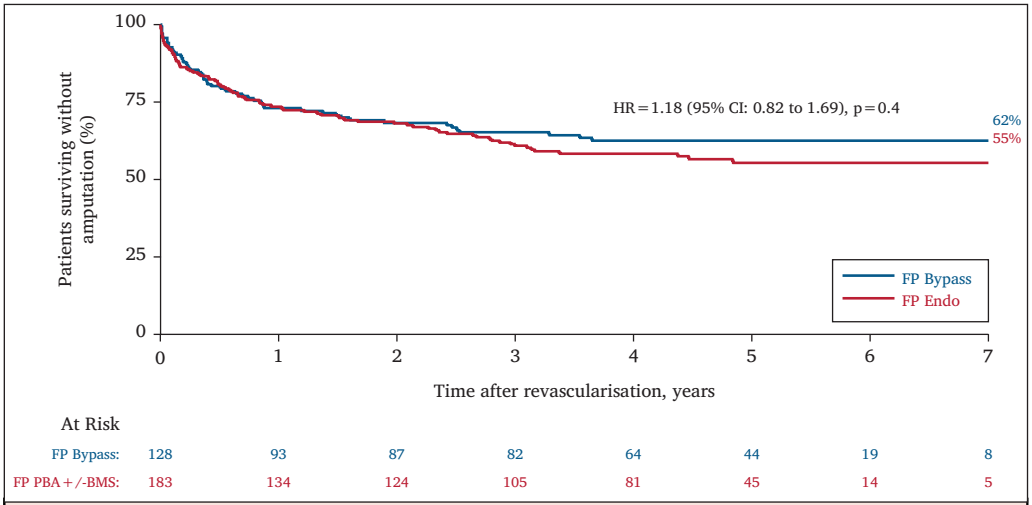

Figure 1. Cumulative Kaplan Meier estimate of amputation free survival in patients undergoing femoropopliteal (FP) bypass and plain balloon angioplasty (PBA) ± bare metal stent (BMS) in the Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial. Endo = endovascular; HR = hazard ratio; CI = confidence interval.

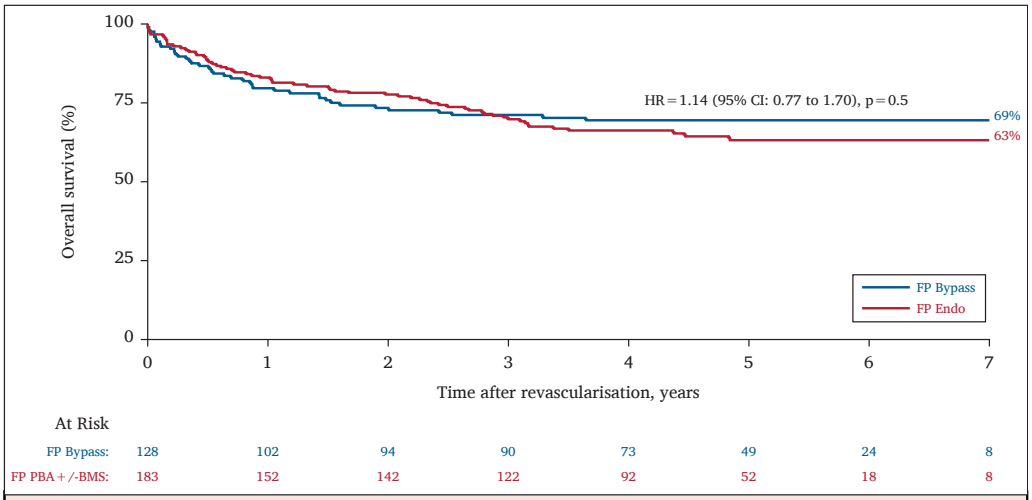

Figure 2. Cumulative Kaplan Meier estimate of overall survival in patients undergoing femoropopliteal (FP) bypass and plain balloon angioplasty (PBA) ± bare metal stent (BMS) in the Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial. Endo = endovascular; HR = hazard ratio; CI = confidence interval.

groups had spent an equivalent median number of days (17 [range 11–28] vs. 17 [range 6–41]; $p = .7$) in hospital. Statin use was low in both groups (OSB 30% vs. PBA ± BMS 37%; $p = .2$). Antiplatelet use was significantly higher in OSB patients (66% vs. 55%; $p = .05$). Although all cause 30 day mortality was not statistically different between the two groups, OSB patients suffered more morbidity; in particular, wound infection (Table 3). PBA ± BMS patients required more surgical interventions within the first 30 days (2% vs. 7%; $p = .06$).

Long-term clinical outcomes OSB vs. PBA ± BMS

There was no difference in AFS (62% vs. 55% [HR 1.18, 95% CI 0.82–1.69; $p = .4$]) (Fig. 1), OS (69% vs. 63% [HR 1.14, 95% CI 0.77–1.70; $p = .5$]) (Fig. 2), or LS (85% vs. 85% [HR 1.09, 95% CI 0.59–2.01; $p = .8$]) between OSB and PBA±BMS. However, FF-MALE (67% vs. 56% [HR 1.51, 95% CI 1.01–2.25; $p = .04$]) (Fig. 3) and FF-R (72% vs. 63% [HR 1.68, 95% CI 1.09–2.60; $p = .02$]) (Fig. 4) were significantly lower following OSB. Resolution of rest pain (85% vs. 76% [HR 0.84, 95% CI 0.63–1.11; $p = .2$]) and wound healing at three years (90% vs. 84% [HR 0.78, 95% CI 0.55–1.10; $p = .2$]) (Fig. 5) were similar in the two groups.

Long-term clinical outcomes VB vs. SynB vs. PBA ± BS

There was no significant difference in AFS (67% vs. 51% vs. 55%; $p = .2$), OS (72% vs. 64% vs. 63%; $p = .4$), and LS (90% vs. 72% vs. 85%; $p = .3$) between VB, SynB, and PBA ± BMS, although the number of SynB was small. FF-

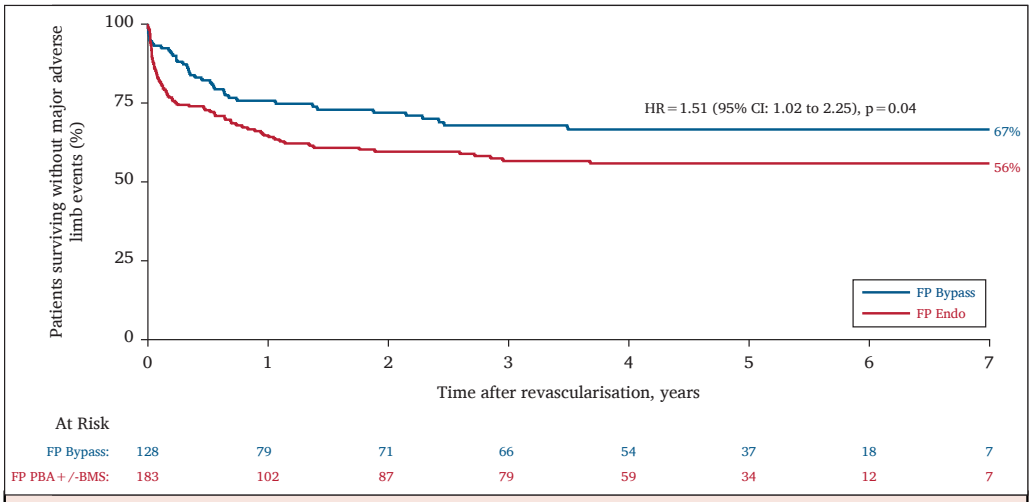

Figure 3. Cumulative Kaplan Meier estimate of freedom from major adverse limb events in patients undergoing femoropopliteal (FP) bypass and plain balloon angioplasty (PBA) ± bare metal stent (BMS) in the Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial. Endo = endovascular; HR = hazard ratio; CI = confidence interval.

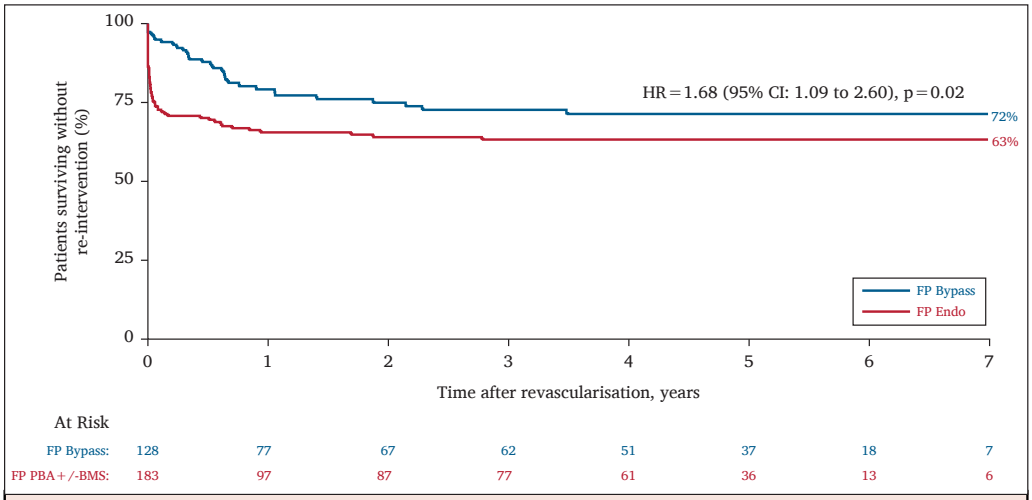

Figure 4. Cumulative Kaplan Meier estimate of freedom from re-intervention in patients undergoing femoropopliteal (FP) bypass and plain balloon angioplasty (PBA) ± bare metal stent (BMS) in the Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial. Endo = endovascular; HR = hazard ratio; CI = confidence interval.

MALE (71% vs. 58% vs. 56%; $p = .02$) was significantly better following VB.

Re-interventions

Overall, 24 (19%) OSB and 63 (34%) PBA ± BMS patients underwent re-intervention, with 38 and 85 re-interventions, respectively (Table 4). There was no difference in the number of inflow procedures performed in each group (7 vs. 8; $p = .2$). Patients in the PBA ± BMS group underwent more secondary bypass procedures ($n = 47$ [55%] vs. $n = 3$ [8%]; $p < .001$) and more repeat angioplasties ($n = 21$ [25%] vs. $n = 5$ [13%]; $p = .1$). OSB patients underwent more angioplasties for in-graft stenosis ($n = 13$ [35%] vs. $n = 1$ [1%]; $p < .001$).

DISCUSSION

The main finding of this BASIL-1 FP subgroup analysis is that although major amputation rates and all cause mortality are similar, primary OSB, especially VB, results in significantly fewer MALE and re-interventions than primary PBA ± BMS. So, although an endovascular first revascularisation strategy may be a less resource intensive (expensive) and morbid option in the short term, in the longer term, this seems unlikely to be the case. Present data add further weight to

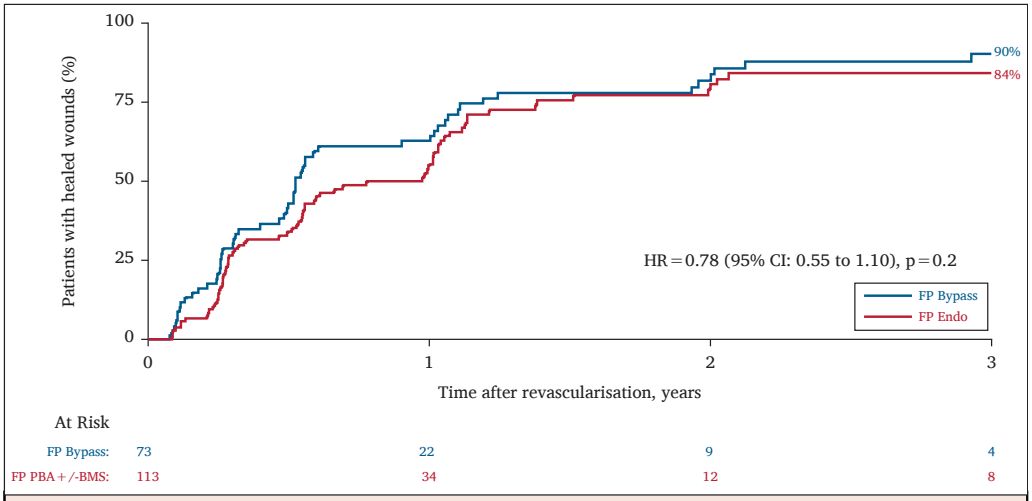

Figure 5. Cumulative Kaplan Meier estimate of wound healing in patients undergoing femoropopliteal (FP) bypass and plain balloon angioplasty (PBA) ± bare metal stent (BMS) in the Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial. Endo = endovascular; HR = hazard ratio; CI = confidence interval.

the argument that, where possible, VB should be offered as the preferred primary revascularisation procedure to most patients presenting with CLTI due to FP disease. This is especially so in standard risk patients (anticipated life expectancy > 2 years) who are more likely to enjoy the long-term benefit of VB and less likely to suffer short-term peri-operative morbidity.[1,5–8] Present data support the previously published BASIL-1 IP subgroup outcomes indicating that the durability and quality of revascularisation are better after VB than after PBA.[2] In this BASIL-1 FP cohort, unlike in the IP cohort, healing of tissue loss and speed of resolution of rest pain were not significantly different between the two groups. This may be because almost a quarter (23%) of the patients who underwent primary FP PBA ± BMS required subsequent OSB for persistent or recurrent symptoms of CLTI. Indeed, CLTI patients presenting with the most severe disease in terms of wound, ischaemia, and infection,[9] seem to be those most likely to enjoy better outcomes following primary VB than primary endovascular intervention. This is especially so given that outcomes following secondary VB after failed primary endovascular intervention are significantly worse than those observed when VB is used as the primary revascularisation procedure.[10,11] The low rates of best medical therapy (antiplatelet and statin use coupled with smoking cessation) often observed in CLTI studies are worthy of discussion. In the present study, only two thirds of patients undergoing OSB were on antiplatelet therapy at randomisation (the rate was 10% lower in PBA ± BMS group) and only about one third of patients in both groups were on a statin. While better medical therapy is likely to improve CLTI outcomes overall, there is no evidence this would have altered the conclusions of BASIL-1 in terms of the recommendation to offer VB first wherever possible. Thus, in a recent large case series,[8] although best medical therapy rates had improved to approximately 80%, the re-intervention rate was 62% for OSB and 52% for PBA at three years. These three year re-intervention data are worse than those observed in BASIL-1 at 7 years. This is an important observation as endovascular enthusiasts often point to the fact that BASIL-1 is now a relatively old trial (patents randomised between 1999 and 2004) and argue that, if BASIL-1 were to be repeated using modern

Table 4. Re-interventions following open surgical bypass and plain balloon angioplasty ± bare metal stent

Re-intervention	Surgical bypass (*n* = 128)	PBA ± BMS (*n* = 183)
Number of patients	24 (19)	63 (34)
Total re-interventions (n)	38	85
Inflow		
Iliofemoral bypass	2 (5)	1 (1)
Iliac PBA ± BMS	2 (5)	4 (5)
Axillofemoral bypass	1 (3)	0 (0)
Aortobifemoral bypass	0 (0)	1 (1)
Common femoral endarterectomy	1 (3)	2 (2)
Femorofemoral crossover	1 (3)	0 (0)
Femoropopliteal revascularisations		
OSB	3 (8)	47 (55)
PBA ± BMS	5 (13)	21 (25)
Graft PBA	13 (34)	1 (1)
Thrombolysis	1 (3)	1 (1)
Embolectomy	3 (8)	2 (2)
Profundaplasty	0 (0)	2 (2)
Graft patch angioplasty	1 (3)	0 (0)
Other		
Graft explanted for infection	2 (5)	1 (1)
Haemostasis	2 (5)	0 (0)
Chemical sympathectomy	1 (3)	2 (2)

Data are *n* (%) unless otherwise indicated. PBA = plain balloon angioplasty; BMS = bare metal stent; OSB = open surgical bypass.

endovascular techniques and technologies, the trial would show a clear advantage in favour of an endovascular first strategy for most, perhaps even all patients. While that is possible, there is no evidence to suggest that such an outcome is likely. Indeed, the evidence suggests that such an outcome would be unlikely. In particular, with regard to drug coated balloons (DCB) and drug eluting stents (DES), there are no data to show that they improve clinical outcomes in patients with CLTI when compared with PBA ± BMS.[12–22] While DCB and DES may be associated with better anatomical outcomes, the great majority of the patients entered into the plethora of industry funded trials had intermittent claudication, underwent treatment of short segment disease, and had short follow ups with little or no reporting of clinical outcomes. Even the small minority of patents in these trials who had CLTI were very largely entered on the basis of rest pain and did not have tissue loss. Other techniques such as laser atherectomy[23] and covered stents[24] have not been widely adopted owing to a lack of evidence demonstrating clinical and cost effectiveness. At the time of writing, there are no published, publicly funded trials comparing DCB/DES with either PBA or OSB in patients with CLTI. As a result, and given their very considerable additional cost, the UK National Institute for Health and Care Excellence (NICE) has recommended against the use of DCB and DES and is awaiting the outcome of ongoing RCTs, specifically BASIL-2[25] and BASIL-3[26] in the UK, and the BEST-CLI trial[27] in the US, before reconsidering the matter. The European Society of Vascular Surgery (ESVS) and European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of patients with peripheral arterial disease[28] specifically state no clinical benefit has been proven for DCB over PBA. Data reported here support the ESC/ESVS guidelines stance that vein bypass surgery for long lesions in patients with CLTI is the first choice method of revascularisation. In conclusion, this BASIL-1 FP subgroup confirms the superiority of VB as the preferred primary FP re-vascularisation procedure for most patients with CLTI. However, the results of further publicly funded, pragmatic RCTs, such as BASIL-2, BASIL-3, and BEST-CLI, are required to help answer the many remaining questions regarding the clinical and cost effectiveness of alternative revascularisation strategies in different subgroups of patients with CLTI.

CONFLICTS OF INTEREST

None.

FUNDING

None.

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Editor's Choice – A Comparison of Clinical Outcomes Between Primary Bypass and Secondary Bypass After Failed Plain Balloon Angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial

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WHAT THIS PAPER ADDS

Angioplasty has been seen as a "free shot" at revascularisation of chronic limb threatening ischaemia. This work suggests that patients requiring secondary bypass after failed initial angioplasty do significantly worse than those who undergo primary bypass surgery.

Objective: Chronic limb threatening ischaemia (CLTI) is a growing global health problem. The UK NIHR HTA funded BASIL trial is still the only randomised controlled trial to have compared a "bypass surgery first" with a "plain balloon angioplasty (PBA) first" strategy for the management of CLTI. In patients who were likely to survive for 2 years and had a suitable vein, primary bypass (PB) was associated with better clinical outcomes. Furthermore, PBA was associated with a high technical and clinical failure rate and many went on to have secondary bypass (SB). This study aimed at comparing clinical outcomes following PB and SB in the BASIL trial.
Methods: Demographic, procedural, and outcome data were obtained from the BASIL case report forms. Outcomes were amputation free survival (AFS), limb salvage (LS), overall survival (OS), and freedom from revascularisation (FFR). The SB cohort comprises patients whose first trial intervention was PBA and who subsequently underwent bypass during follow up. The PB cohort comprises those patients whose first trial intervention was bypass.
Results: The 190 PB and 49 SB patients were well matched except that the SB patients were more likely to be current smokers. At a median of 7 years, PB was associated with better AFS (PB 60% vs. SB 40%; HR 1.58, $p = .04$), LS (PB 85% vs. SB 73%, $p = .06$), and OS (PB 68% vs. 51%, $p = .06$). FFR was equivalent (PB 53% vs. 53%, $p = .3$).
Conclusion: In the BASIL trial, clinical outcomes following PB were significantly better than in patients undergoing SB after failed PBA. Prior to treating patients with CLTI with primary PBA, clinicians should consider that if this should fail, the outcome of attempted subsequent bypass is likely to be significantly worse than if PB were attempted.

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INTRODUCTION

Although chronic limb threatening ischaemia (CLTI) is a growing global health problem,[1,2] the evidence underpinning the choice of revascularisation strategy remains poor. The UK NIHR HTA funded Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) trial remains the only randomised controlled trial (RCT) to have compared a "bypass surgery first" with a "plain balloon angioplasty (PBA) first" strategy for CLTI resulting from infra-inguinal disease.[3] An intention to treat analysis (ITT) of BASIL outcome data showed that, in patients who were likely to survive for at least 2 years and who had a suitable vein, primary bypass (PB) led to better clinical outcomes than primary PBA. Furthermore, primary PBA was associated with a high technical and clinical failure rate such that many of the patients went on to have secondary bypass (SB). Despite this 'level 1' evidence in support of surgical bypass as the preferred revascularisation strategy for patients with a suitable vein, enthusiasm for an endovascular first approach to most, perhaps even all, patients with CLTI continues to grow.[4] As a result, vein bypass is increasingly being viewed as a secondary, salvage procedure to be performed when all endovascular revascularisation options have been exhausted.[5,6] There are surprisingly few published reports of outcomes following SB for failed

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endovascular revascularisation. Furthermore, in the few studies that are available, patient numbers are often small, patients were not randomised, and patients with intermittent claudication and CLTI are often conflated.[7–9] This topic was briefly reported in the analysis by treatment received, only SB within 8 weeks of primary PTA were included and only AFS was reported but no further in depth analyses were performed.[10] The aim of this study, therefore, was to compare clinical outcomes following PB, and all SB after failed primary PBA in the BASIL trial.

METHOD

The BASIL trial methodology has been published previously.[3] Ethical approval was obtained from the Multi-Centre Research Ethics Committee for Scotland. Briefly, patients with CLTI resulting from infra-inguinal disease were randomised to either a PB or primary PBA revascularisation strategy between 1999 and 2004. Patients were followed up until death or the censor date of July 1, 2007. This provided all surviving patients with a minimum of 3 years follow up (median 51, range 0—92 months).

BASIL trial case report forms (CRF) were interrogated to obtain demographic, procedural, and outcome data including amputation free survival (AFS), limb salvage (LS), overall survival (OS), and freedom from re-intervention (FFR) defined as any further revascularisation of the index limb. The SB cohort comprised patients whose first trial intervention was PBA and who subsequently underwent SB (with any conduit) at any point during trial follow up. The PB cohort comprised those patients whose first trial intervention was PB with any conduit. Time to event analyses are presented over a 7 year period using Kaplan-Meier plots. Hazard ratios were used to detect statistically important differences in outcomes using 95% CI. Differences between the cohorts were compared using *t* test, chi-squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

RESULTS

There were 238 attempted primary PBA in the BASIL trial; of these, 69 patients went on to have a secondary intervention, 17 had a tertiary intervention, and seven had a fourth intervention. Twenty-five (36.2%) of the secondary interventions were PBA; of these, three (12%) subsequently underwent SB. The remaining 46 SBs were performed after failed primary PBA. In BASIL, 190 patients underwent PB.

The 190 PB and the 49 SB patients were well matched at the time of randomisation in terms of baseline demographics except that the SB patients were more likely to be current smokers (Table 1). Medical management was also similar (Table 2). Of those who went on to have SB, 49% (24/49) had a technically successful primary PBA. Tissue loss was present in most patients in both groups (ulcer 62% vs. 69%, $p = .3$, gangrene 34% vs. 29% $p = .5$). The median time interval between primary PBA and SB was 0 months (range 0—20 months). Of those who underwent PB, 9.5% (18/190) underwent secondary PTA, 94.4% (17/18) of these were for vein graft stenosis and 100% survived with their limb at the end of trial follow up.

At a median of 7 years, PB was associated with significantly better AFS (PB 60% vs. SB 40%; HR 1.58, 95% CI 1.03—2.44, $p = .04$). Although LS and OS did not reach statistical significance there was a trend to better outcomes in the PB group (LS; PB 85% vs. SB 73%; HR 1.86, 95% CI 0.97—3.58, $p = .06$, and OS; PB 68% vs. 51%; HR 1.57, 95% CI 0.97—2.54, $p = .06$). FFR was the same in both groups (PB 53% vs. 53%; HR 1.43, 95% CI 0.74—2.74, $p = .3$) except that, of course, by definition, those patients undergoing SB were all undergoing a re-intervention (Figs. 1—4).

Procedural data were available for all patients who underwent SB (Table 3). All SB were deemed technically successful at the end of the procedure. Four (8%) SB were prosthetic compared with 22% (41/190) PB ($p = .03$). The absolute amputation rate to the end of follow up was 15.3% vs. 26.5% ($p = .06$). The distal anastomosis was not statistically different between PB and SB with 68% (130/190) versus 64% (31/49) being to the popliteal artery ($p = .4$). There was no significant difference between PB and SB in terms of 30 day morbidity and mortality (Table 4).

DISCUSSION

In the BASIL trial, 190 patients underwent PB and, of the 238 patients who underwent an attempt at primary PBA, 49 (21%) went on to require a SB at some point during the trial follow up. The key finding of the present study is that PB was associated with statistically significantly better AFS and a strong trend ($p = .06$) towards better LS and OS. It is accepted that the SB group are a group of failures, which suggests they are different to the PB group, the challenge for this analysis is to identify why. It is also accepted that the BASIL trial was not powered to investigate this relationship, nevertheless it is an important relationship that is poorly understood. The two cohorts were well matched in terms of baseline demographics and medical therapy at randomization, PB patients were more likely to be current smokers and have a history of TIA; however, it is noted that this group was observed to have better clinical outcomes. This suggests that the observed differences are not related to the patient's medical characteristics. The anatomical burden of disease is certainly influential in type of revascularisation required and outcome of said intervention. Bollinger analysis of these groups suggests that there is no difference in burden or distribution of disease between these groups (Table 5).

The appropriateness of the observed trend in recent years towards an endovascular first strategy for most, perhaps even all, CLTI is now being challenged.[11–13] However, although several groups have reported outcomes following PB and primary endovascular revascularisation, few have analysed the effect of failed endovascular intervention on the success of SB. But, these reports, taken with the data from the BASIL trial presented here, indicate that primary endovascular intervention is not the "free shot" that it has so often been claimed to be.

Table 1. Comparison of primary and secondary bypass patients in the BASIL trial.

		Primary bypass	Secondary bypass	*p* value
Number of patients		190	49	
Age, years	Mean (SD)	72 (9.3)	73 (7.3)	0.4
	Range	39–98	58–87	
Gender	Male	127 (66%)	28 (57%)	0.2
Limb	Left	105 (55%)	27 (55%)	1.0
	Right	85 (45%)	22 (45%)	
ABPI	Mean (SD)	0.5 (0.18)	0.48 (0.11)	0.5
Smoker	Never	30 (16%)	12 (24%)	0.05
	Ex	86 (45%)	13 (27%)	
	Current	74 (39%)	24 (49%)	
Diabetes	No	113 (60%)	23 (47%)	0.2
	IDDM	31 (16%)	12 (24%)	
	NIDDM	46 (24%)	14 (29%)	
Hypercholesterolemia	No	45 (24%)	11 (22%)	0.6
	Yes, untreated	22 (11%)	3 (6%)	
	Yes, treated	66 (35%)	17 (35%)	
	No record of assessment	57 (30%)	18 (37%)	
Hypertension	No	77 (41%)	19 (39%)	0.8
	Yes, untreated	12 (6%)	2 (4%)	
	Yes, treated	101 (53%)	28 (57%)	
Mobility	Independent	91 (48%)	22 (45%)	0.8
	Cane	79 (41%)	22 (45%)	
	Prosthesis	2 (1%)	1 (2%)	
	Wheelchair	13 (7%)	4 (8%)	
	Bedbound	5 (3%)	0 (–)	
Myocardial infarction	Yes	26 (14%)	8 (16%)	0.6
Angina	No	153 (81%)	44 (90%)	0.2
	Yes, on exercise	31 (16%)	3 (6%)	
	Yes, at rest	6 (3%)	2 (4%)	
TIA	Yes	19 (10%)	1 (2%)	0.07
Stroke	Yes	25 (13%)	6 (12%)	0.9
Rest pain	Yes	170 (89%)	45 (92%)	0.6
Ulcer	Yes	117 (62%)	34 (69%)	0.3
Gangrene	Yes	64 (34%)	14 (29%)	0.5
Creatinine	N	186	45	
	Mean (SD)	116 (79.4)	111 (62.0)	0.7
	Range	50–702	40–452	

IDDM = insulin dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus; TIA = transient ischaemic attack; ABPI = ankle brachial pressure index.

Although BASIL trial data are often said to be outdated and so no longer relevant to current practice, in reality, there is no evidence that is the case.[8] For example, Darling and colleagues recently studied 2869 patients undergoing lower limb revascularisation for CLTI and concluded that PB resulted in better outcomes in wound healing, FFR, and OS; and that patients undergoing SB had higher rates of further intervention.[14] In another study, Jones and co-workers

Table 2. Medical management in patients undergoing primary and secondary bypass in BASIL.

		Primary bypass	Secondary bypass	*p* value
Number of patients		190	49	
Antiplatelet	None	52 (27%)	17 (35%)	0.2
	Single	111 (59%)	24 (49%)	
	Double	2 (1%)	1 (2%)	
	Antiplatelet + other	15 (8%)	1 (2%)	
	Other	10 (5%)	6 (12%)	
Antihypertensive	None	81 (43%)	18 (37%)	0.3
	One	53 (28%)	19 (39%)	
	Two	40 (21%)	6 (12%)	
	Two or more	16 (8%)	6 (12%)	
Statin	None	123 (65%)	31 (63%)	0.8
	Yes	67 (35%)	18 (37%)	
Diabetes treatment	None	131 (69%)	25 (51%)	0.1

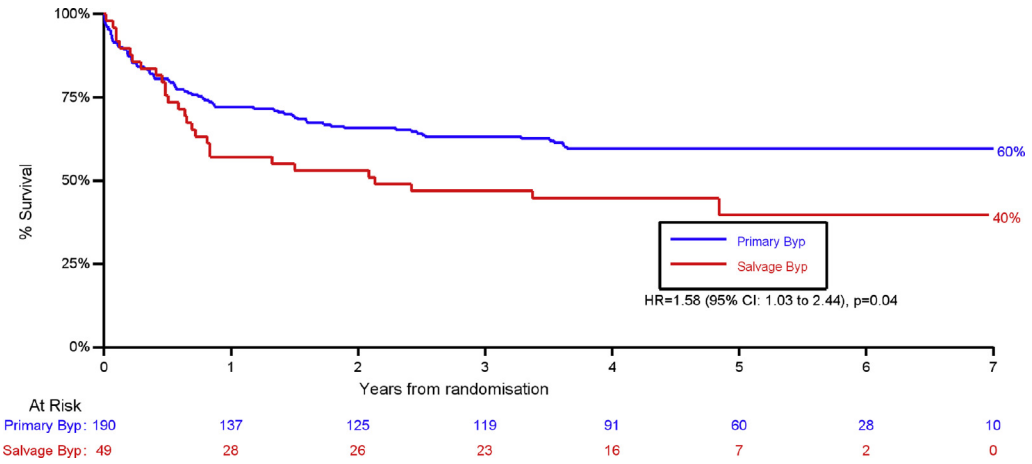

Figure 1. Comparison of amputation free survival in patients undergoing primary and secondary bypass in the BASIL trial.

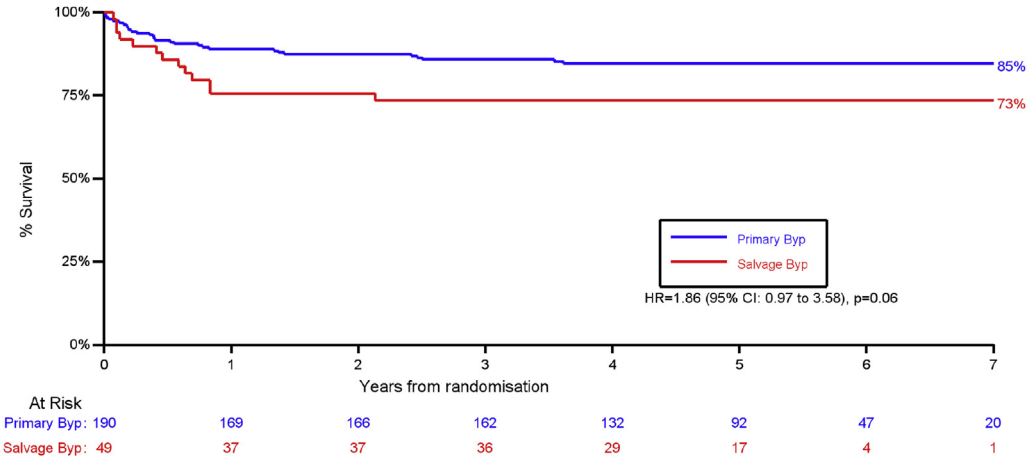

Figure 2. Comparison of limb salvage in patients undergoing primary and secondary bypass in the BASIL trial.

analysed 1154 CLTI patients undergoing SB and concluded that these patients had worse MALE, FFR, OS, and AFS.[15]

Interestingly, although more BASIL patients in the PB group underwent synthetic bypass (PB 22%, SB 8%), overall, the clinical results of PB were far superior to those observed after SB. In the UK, synthetic grafts are almost always reserved for those patients with no usable leg or arm vein.[16–18] As such, it could be argued that patients undergoing prosthetic bypass should have been removed from this analysis. However, the decision was made to include them as a proportion of CLTI patients requiring bypass will not have useable veins. Approximately a third of the

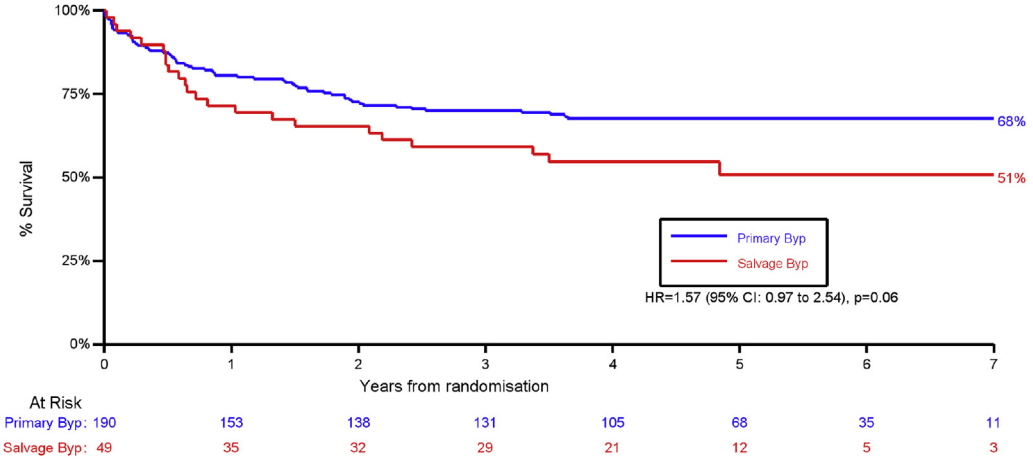

Figure 3. Comparison of overall survival in patients undergoing primary and secondary bypass in the BASIL trial.

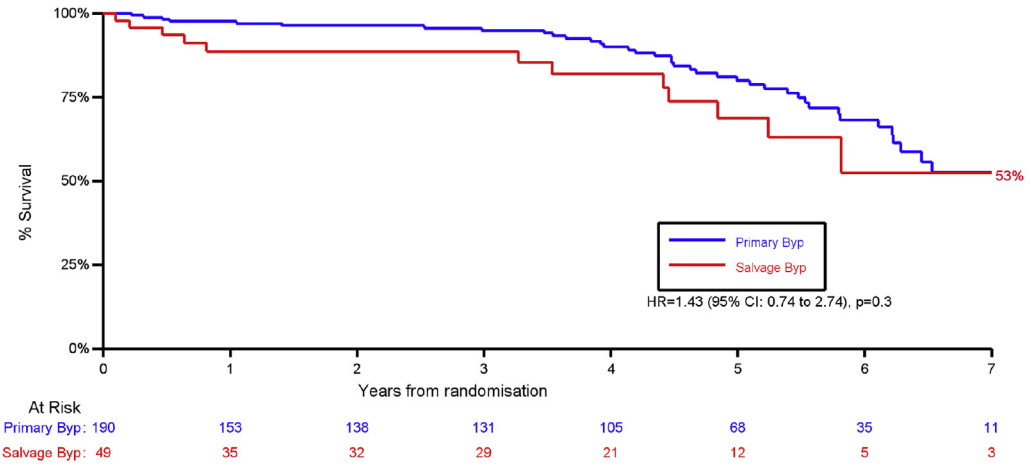

Figure 4. Comparison of freedom from re-intervention in patients undergoing primary and secondary bypass in the BASIL trial.

Table 3. Frequencies of proximal and distal anastomosis location for primary and secondary bypass.

		Primary bypass	Secondary bypass	*p* value
Number of patients		190	49	
Distal anastomosis	Not known	2 (1%)	0 (–)	0.4
	AKPA	63 (33%)	10 (20%)	
	BKPA	67 (35%)	21 (44%)	
	PTA	17 (9%)	2 (4%)	
	ATA	20 (11%)	9 (18%)	
	PA	17 (9%)	6 (12%)	
	DP	2 (1%)	0 (–)	
	TPS	1 (0.5%)	1 (2%)	
	DPP	1 (0.5%)	0 (–)	
Conduit	Vein	149 (78%)	45 (92%)	0.03
	Synthetic	41 (22%)	4 (8%)	

AKPA = above knee popliteal artery; BKPA = below knee popliteal artery; PTA = posterior tibial artery; ATA = anterior tibial artery; PA = peroneal artery; DP = dorsalis pedis; TPS = tibial peroneal stem; DPP = dual popliteal and pedal.

Table 4. Mortality and morbidity (30 days) in patients undergoing primary and secondary bypass in BASIL.

	Primary bypass	Secondary bypass	*p* value
Number of patients	190	49	
Angina	2 (1%)	0 (–)	0.5
MI	8 (4)	2 (4)	1.0
TIA	0 (–)	0 (–)	–
CVA	1 (0.5%)	1 (2%)	0.3
Haematoma (no surgery)	8 (4%)	1 (2%)	0.5
Haematoma (surgery)	3 (2%)	0 (–)	0.4
LRTI	6 (3%)	1 (2%)	0.7
UTI	9 (5%)	1 (2%)	0.4
False aneurysm (no surgery)	1 (0.5%)	0 (–)	0.6
False aneurysm (surgery)	0 (–)	0 (–)	–
30 day mortality	11 (6%)	4 (8%)	0.5
30 day morbidity and mortality	83 (44%)	19 (39%)	0.5
MACE	17 (9%)	6 (12%)	0.5

MI = myocardial infarction; TIA = transient ischaemic attack; CVA = cerebrovascular accident; LRTI = lower respiratory tract infection; UTI = urinary tract infection; MACE = major adverse cardiac event.

patients in each group underwent infra-popliteal bypass and so this can be discounted as a cause of the differences observed between PB and SB.

Going forward, it will be important to determine whether drug coated balloons and drug eluting stents will increase the clinical success of primary endovascular intervention for CLTI. The ongoing UK NIHR HTA funded BASIL 2 and 3 trials,[19,20] and US NIH funded BEST CLI trial,[21] will together recruit more than 3500 CLTI patients undergoing PB and primary endovascular intervention and will address this and many other important question so informing evidence based revascularisation (EBR).

Table 5. Comparison of Bollinger scores between primary and secondary bypass.

Segment	Stats	PB	SB	*p* value
Profunda	Mean (SD)	2.4 (3.4)	2.5 (3.6)	0.828
Proximal SFA	Mean (SD)	6.7 (5.6)	5.8 (5.3)	0.3
Distal SFA	Mean (SD)	9.2 (5.4)	10.4 (5.0)	0.2
Proximal POP	Mean (SD)	6.6 (5.7)	7.3 (6.3)	0.5
Distal POP	Mean (SD)	3.7 (5.1)	3.7 (5.1)	1.0
TPT	Mean (SD)	4.1 (5.8)	2.8 (5.0)	0.2
Proximal PT	Mean (SD)	8.5 (7.0)	8.7 (7.0)	0.9
Distal PT	Mean (SD)	9.7 (6.5)	9.2 (6.9)	0.7
Proximal AT	Mean (SD)	6.9 (6.5)	8.5 (7.0)	0.2
Distal AT	Mean (SD)	7.3 (6.9)	8.7 (7.0)	0.3
Proximal PERO	Mean (SD)	4.8 (5.8)	4.2 (5.9)	0.6
Distal PERO	Mean (SD)	5.5 (6.5)	2.2 (5.0)	0.005
Total FP score	Mean (SD)	25.7 (9.9)	26.3 (9.0)	0.7
Total IP score	Mean (SD)	45.3 (24.8)	46.3 (26.6)	0.8
Total score	Mean (SD)	71.1 (26.4)	72.7 (26.6)	0.8

SFA = superficial femoral artery; POP = popliteal artery; TPT = tibio-peroneal trunk; PT = posterior tibial artery; AT = anterior tibial artery; PERO = peroneal artery.

CONCLUSION

In the BASIL trial, clinical outcomes following PB were significantly better than in patients undergoing SB after failed PBA. Prior to treating patients with CLTI by primary PBA, clinicians should consider that if this should fail, the outcome of attempted subsequent bypass is likely to be significantly worse than if PB were attempted.

CONFLICT OF INTEREST

None.

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Comparison of femoropopliteal plain balloon angioplasty for chronic limb-threatening ischemia in the BASIL trial and in a UK contemporary series

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ABSTRACT

Background: Since the turn of the millennium, there has been a worldwide trend towards an endovascular-first strategy where possible revascularization strategy for chronic limb-threatening ischemia. There is concern that this may be inappropriate and can result in net patient harm. The aim of this study, therefore, is to compare important clinical outcomes following femoropopliteal plain balloon angioplasty (FP-PBA), with selective use of bare metal stents (BMSs), in a contemporary series (CS) of patients treated in our unit between 2009 and 2014 with those observed following FP-PBA ± BMS in the United Kingdom National Institute of Health Research Health Technology Assessment-funded Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL-1 [B1]) trial (treated 1999-2004).

Methods: Baseline and clinical outcome data (amputation-free survival [AFS], overall survival [OS], limb salvage, freedom from reintervention, and freedom from major adverse limb events) were obtained from prospectively gathered hospital data and B1 trial case record forms.

Results: There were 237 CS and 218 B1 patients. CS patients were older (77 vs 73 years; $P = .0002$). B1 patients were more likely to be current smokers, less likely to be on best medical therapy, and underwent more extensive endovascular interventions. CS had more hospital admissions (4 vs 2; $P < .0001$) before they reached their primary endpoint (AFS). Immediate technical success was nonsignificantly higher in the CS patients (87% vs 83%; $P = .2$). BMS were used in 20 CS (8%) and 2 B1 (1%) patients ($P = .0002$). AFS (hazard ratio, 0.64; 95% confidence interval, 0.49-0.82; $P = .0005$) and OS (hazard ratio, 0.58; 95% confidence interval, 0.44-0.76; $P = .0001$) were significantly worse in the CS cohort. There was no significant difference in limb salvage, freedom from reintervention, or freedom from major adverse limb events.

Conclusions: Patients with chronic limb-threatening ischemia managed in our unit (2009-2014) by means of a FP-PBA ± BMS first (where possible) revascularization strategy experienced significantly worse AFS and OS than patients treated with FP-PBA ± BMS in the B1 trial 10 years earlier (1999-2004). (J Vasc Surg 2021;74:1948-55.)

Keywords: Peripheral vascular disease; Chronic limb-threatening ischemia; Angioplasty; Endovascular

Chronic limb-threatening ischemia (CLTI) is estimated to affect 500 to 1000 per million population in developed countries and, although reliable epidemiologic data are limited, it is widely accepted that the incidence of CLTI is increasing rapidly in the so-called emerging economies and developing world.[1] The prognosis for most people with CLTI remains poor in terms of limb loss and premature mortality.[2] Unfortunately, the evidence base underpinning the treatment of CLTI, especially regarding the preferred method of revascularization, also remains poor. There has been a nonevidence-based worldwide trend towards an endovascular-first where possible revascularization strategy for CLTI.[3] This is despite the only available level 1 evidence from the United Kingdom (UK) National Institute of Health Research Health Technology Assessment-funded Bypass vs Angioplasty for Severe Ischaemia of the Leg randomized trial (BASIL-1 [B1]) showing that, in average-risk patients with CLTI, a bypass-first revascularization strategy is associated with significantly better long-term clinical outcomes.[4] This finding has been confirmed in more recent nonrandomized studies.[5-10] Like many others,[11] our unit has increasingly employed an endovascular-first where possible revascularization strategy in patients presenting with CLTI, reserving bypass surgery for those patients who either are not suitable for or fail endovascular intervention. However, there is increasing concern that such a strategy may be inappropriate and can result in net patient harm. We

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therefore believed it was important for us to investigate whether our current strategy was providing acceptable clinical outcomes when compared with those reported in B1, which remains the only published randomized dataset. The aim of the current study, therefore, was to compare outcomes following femoropopliteal plain balloon angioplasty (FP-PBA) ± bare metal stents (BMSs) in a contemporary series (CS) of patients with CLTI treated in our unit between 2009 and 2014 with those observed in patients randomized in B1 to FP-PBA ± BMSs between 1999 and 2004.

METHODS

Baseline and clinical outcome data (amputation free survival [AFS], overall survival [OS], limb salvage [LS], freedom from reintervention [FF-R], and freedom from major adverse limb events [FF-MALE]) in CS and B1 patients undergoing FP-PBA ± BMS as part of their primary endovascular revascularization for CLTI were obtained from prospectively gathered hospital databases and B1 case record forms. Patients were included if they were suffering with CLTI (ulceration, gangrene, ischemic rest pain) and met the anatomical inclusion criteria for entry into the BASIL-3 trial; namely, they had predominantly FP disease ± infra-popliteal (IP) disease. B1 patients underwent their intervention between August 12, 1999 and June 23, 2004, and CS patients about 10 years later, between January 1, 2009 and December 31, 2014. B1 data were censored on July 1, 2007 and CS data on May 31, 2017.

FF-R was defined as absence of attempted revascularization of the index limb or interventions relating to complications of the primary procedure. Minor amputations (distal to tarsal bones) were not considered a reintervention as they are more likely to be a consequence of the severity of the presenting clinical condition rather than type of revascularization. MALE comprised any attempt at revascularization or a major amputation (above ankle) of the index limb during the study period. Technical success was defined by the responsible interventionalist based upon successful device use and satisfactory post-intervention angiographic appearance.

As part of the BASIL-1 trial protocol and statistical analysis plan, baseline and postintervention angiograms were collected, and these were Bollinger-scored[12] in order to characterize the anatomical burden of disease. Of the 218 B1 patients included in this study, 196 had Bollinger scores. CS patients were also Bollinger-scored for comparison. More recently, the Global Vascular Guidelines[13] introduced the Global Anatomic Staging System (GLASS) score. CS and BI were also GLASS-scored to provide an up-to-date comparison of the anatomic extent of baseline disease.

Ethical approval was granted for the BASIL trial (ISRCTN − 45398889); no ethical approval was required for the CS data collection as this is classed as an audit of clinical outcomes. Patient consent was obtained prior to entry into the BASIL trial, and was not required for those included in the CS.

Baseline differences between the CS and B1 cohorts were compared using the t test, χ^2 test, Fisher exact test, and Wilcoxon rank sum test according to distribution of data; Cox regression was used to calculate statistically important differences in AFS, OS, LS, FF-R, and MALE using hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analysis was performed using SAS v 9.4 (SAS Institute, Cary, North Carolina).

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Employing an endovascular-first strategy for revascularization of femoropopliteal induced chronic limb-threatening ischemia has led to significantly worse amputation-free survival in a contemporary series of patients compared with that observed in the BASIL trial.
- **Take Home Message:** Despite advances in endovascular technology and techniques, current clinical outcomes do not support a shift to an endovascular-first strategy for treating chronic limb-threatening ischemia.

RESULTS

There were 237 and 218 patients in the CS and B1 cohorts, respectively. CS patents were older (77 vs 73 years; $P = .0002$) but otherwise (apart from higher levels of congestive cardiac failure in the CS cohort [10% vs 4%]), the cohorts were generally well-matched in terms of baseline characteristics and risk factors (Table I). B1 patients were more likely to be current smokers and less likely to be on best medical therapy (BMT). B1 patients had a significantly higher burden of FP disease at baseline according to Bollinger (total score 44.8 vs 39.4; $P = .031$) and there was a trend ($P = .06$) to more advanced GLASS FP grade. B1 patients were also more likely to have more than 3 arterial segments treated (12% vs 25%; $P = .004$; Table II). CS patients were more likely to suffer from 30-day myocardial infarction (5% vs 1%; $P = .01$) and cerebrovascular event (6% vs 2%; $P = .03$). However, 30-day mortality was not significantly different between the 2 groups (4% vs 3%; $P = .5$). CS patients spent less time in hospital during their index admission (3 vs 8 days; $P < .0001$) and over the first 12 months (12 vs 19 days; $P = .002$). However, CS patients spent an equivalent amount of time in hospital (31 vs 27 days; $P = .8$) and had more hospital admissions (4 vs 2; $P < .0001$) before they reached the primary endpoint (AFS, death from any cause, or major amputation, whichever occurred first). Immediate technical success, as

Table I. Baseline data in the CS and B1 cohorts

	CS (n = 237), No. (%)	B1 (n = 218), No. (%)	*P*
Age, years			
Mean (SD)	77 (11.1)	73 (8.6)	.0002
Range	38-99	46-95	
Gender			
Male	130 (55)	118 (54)	.9
Clinical presentation			
Rest pain only	75 (32)	79 (36)	<.0001
Tissue loss only	131 (55)	15 (7)	
Both	31 (13)	123 (56)	
Neither	0 (0)	1 (1)	
Smoking status			
Never	24 (10)	0 (–)	<.0001
Ex	26 (11)	47 (21)	
Current	36 (15)	69 (32)	
Unknown	151 (64)	102 (47)	
Creatinine			
Mean (SD)	99 (64.5)	109 (56.5)	.1
Range	0-642	28-633	
Unknown	0	12	
DM			
No	152 (64)	127 (58)	.2
Yes	85 (36)	91 (42)	
CHF			
No	214 (90)	209 (96)	.02
Yes	23 (10)	9 (4)	
HTN			
No	83 (35)	82 (38)	.6
Yes	154 (65)	136 (62)	
CAD			
No	180 (76)	158 (72)	.4
Yes	57 (24)	60 (28)	
COPD			
No	210 (89)	203 (93)	.1
Yes	27 (11)	15 (7)	
Statin			
No	75 (32)	140 (64)	<.0001
Yes	147 (62)	78 (36)	
Unknown	15 (6)	0 (–)	
Other lipid-lowering drug			
No	211 (89)	216 (99)	<.0001
Yes	11 (5)	2 (1)	
Unknown	15 (6)	0 (–)	
Antiplatelet			
No	69 (29)	97 (45)	<.0001
Yes	154 (65)	121 (55)	
Unknown	14 (6)	0 (–)	
Anticoagulant			
No	191 (81)	204 (94)	<.0001
Yes	31 (13)	14 (6)	
Unknown	15 (6)	0 (–)	
ACE inhibitor			
No	122 (52)	152 (70)	<.0001
Yes	100 (42)	66 (30)	
Unknown	15 (6)	0 (–)	
Beta blocker			
No	167 (71)	193 (89)	<.0001
Yes	55 (23)	25 (11)	
Unknown	15 (6)	0 (–)	

ACE, Angiotensin-converting enzyme; *B1*, BASIL-1; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *CS*, contemporary series; *DM*, diabetes mellitus; *HTN*, hypertension; *SD*, standard deviation.

adjudicated by the interventional radiologist performing the procedure, was nonsignificantly higher in the CS cohort (87% vs 83%; $P = .2$). BMSs were used in 20 CS (8%) and 2 B1 (1%) patients ($P = .0002$). AFS (HR, 0.64; 95% CI, 0.49-0.82; $P = .0005$; Fig 1) and OS (HR, 0.58; 95% CI, 0.44-0.76; $P = .0001$; Fig 2) were highly significantly worse in the CS cohort than in the B1 cohort. There was no significant difference in LS (HR, 0.75; 95% CI, 0.48-1.18; $P = .2$; Fig 3), FF-R (HR, 1.19; 95% CI, 0.86-1.66; $P = .3$), or FF-MALE (HR, 1.02; 95% CI, 0.76-1.37; $P = .9$; Fig 4). Although there was no overall difference in reintervention rates between the 2 cohorts, B1 patients were more likely to undergo bypass surgery, as opposed to a further endovascular intervention, as their second revascularization procedure (69% vs 18%; $P \leq .001$).

DISCUSSION

The main finding from the present study is that, despite the widely averred advances in endovascular technologies and greater familiarity with endovascular techniques, important clinical outcomes after FP-PBA ± BMS for CLTI in our unit between 2009 and 2014 are no better than they were 10 years earlier in the B1 trial between 1999 and 2004. Indeed, disappointingly, AFS and OS are now very significantly worse.

Although some may argue that this is because patients are now more comorbid with more extensive disease, this is not borne out by the present data. Thus, although CS patients were older, the 2 cohorts were well-matched in terms of baseline comorbidities and vascular risk factors. Furthermore, B1 patients were more likely to be current smokers and less likely to be on BMT. However, only two-thirds of CS patients were on BMT, indicating that a large proportion of patients under our care with CLTI in

Table II. Summary of Bollinger and GLASS scores by cohort

Arterial segment	CS Endo	B1 Endo	*P*
Profunda	0.76 (2.6)	2.43 (3.8)	<.000
Proximal SFA	4.3 (4.8)	6.6 (5.4)	<.000
Distal SFA	6.6 (5.3)	9.9 (5.0)	<.000
Proximal popliteal	6.8 (5.4)	7.1 (5.7)	.520
Distal popliteal	3.9 (5.2)	3.2 (4.5)	.145
TPT	3.5 (5.5)	3.6 (4.9)	.787
AT proximal	5.9 (6.8)	6.8 (6.0)	.144
AT distal	5.7 (7.1)	7.3 (6.7)	.019
PT proximal	7.8 (8.1)	8.8 (6.2)	.131
PT distal	8.0 (8.3)	9.4 (6.4)	.037
Peroneal proximal	4.5 (6.2)	4.9 (5.3)	.425
Peroneal distal	4.2 (6.5)	4.4 (5.6)	.682
Total score	61.8 (32.0)	73.8 (27)	.000
Femoropopliteal total score	39.4 (28.2)	44.8 (23.4)	.031
Infra-popliteal total score	22.4 (12.3)	29.2 (11.1)	<.000
FP GLASS grade	237	196	
0	0 (0)	1 (0.5)	
1	13 (5.5)	21 (10.7)	
2	29 (12.2)	35 (17.9)	
3	62 (26.2)	43 (21.9)	
4	133 (56.1)	96 (49.0)	.060
IP GLASS Grade			
0	166 (70.0)	137 (69.9)	
1	15 (6.3)	22 (11.2)	
2	23 (9.7)	18 (9.2)	
3	11 (4.6)	5 (2.6)	
4	22 (9.3)	11 (5.6)	.185
GLASS Stage			
1	30 (12.7)	38 (19.4)	
2	64 (27.0)	54 (27.6)	
3	143 (60.3)	103 (52.6)	.137

AT, Anterior tibial artery; *B1,* BASIL-1; *CS,* contemporary series; *FP,* femoral-popliteal; *GLASS,* Global Anatomic Staging System; *IP,* infra-popliteal; *PT,* posterior tibial artery; *SFA,* superficial femoral artery; *TPT,* tibio-peroneal trunk.
Continuous data are presented as mean (standard deviation) and categoric data as number (percentage).

the period 2009 to 2014 were still not receiving optimal medical therapy.

Although B1 patients had more extensive endovascular interventions and also had a significantly higher anatomic burden of baseline disease, as determined by overall Bollinger score and GLASS FP grade, there was no significant difference in immediate technical success rates.[14,15] Of note, more CS patients had BMSs as an adjunct to PBA, and this may help explain the small improvement observed.[16,17] However, even in the CS, BMSs were used infrequently and then predominantly to improve a suboptimal PBA outcome rather than as a primary treatment option.[18-20] We believe that the use of BMSs in the CS to be typical of UK practice and in line with UK National Institute for Health and Care Excellence guidelines.[21]

Interestingly, we observed a markedly different approach to further revascularization after failed primary endovascular intervention. In B1, most patients underwent bypass surgery as their further procedure; whereas in the CS, most patients had a further endovascular procedure. This did not result in a significant difference in LS. However, there was a trend towards improved OS after 3 years in favor of the B1 patients. This did not reach statistical significance and may be a result of the CS patients being significantly older at first treatment.

It is obviously disappointing to report that the results of PBA ± BMS in our unit during the period from 2009 to 2014 were not superior in terms of limb-based

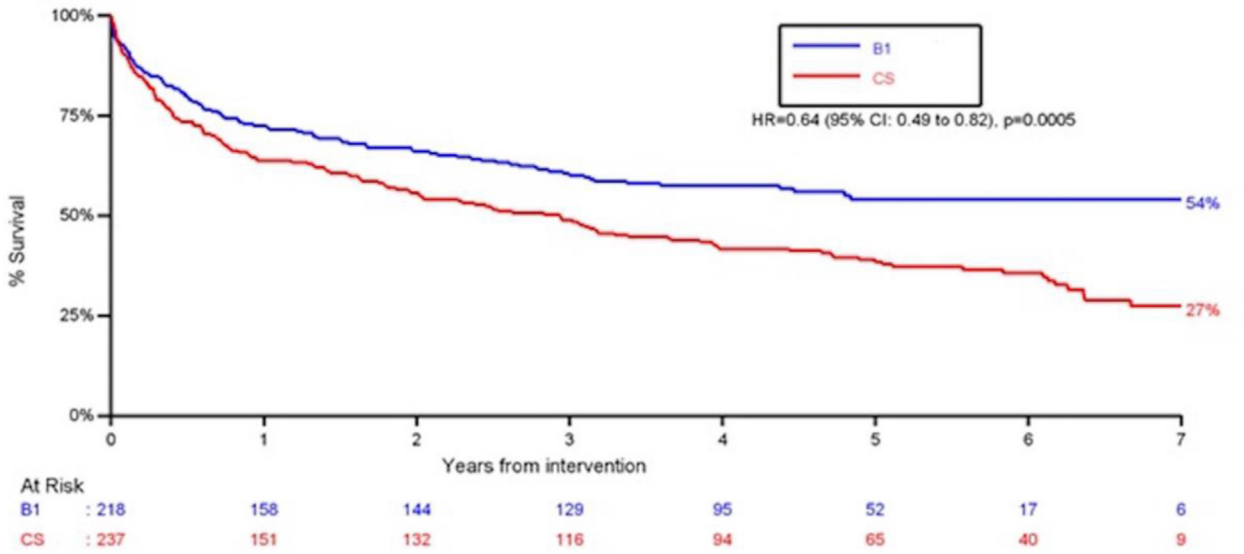

Fig 1. Amputation-free survival (AFS) in contemporary series (*CS*) and BASIL-1 (*B1*) patients undergoing femoropopliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS). *CI,* Confidence interval; *HR,* hazard ratio.

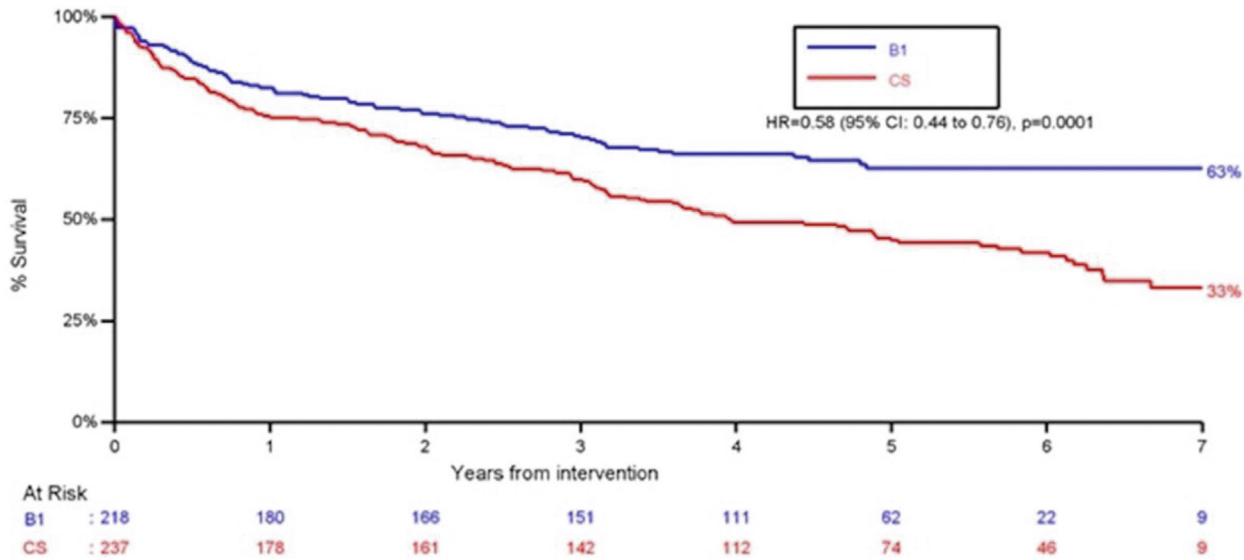

Fig 2. Overall survival (OS) in contemporary series (*CS*) and BASIL-1 (*B1*) patients undergoing femoropopliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS). *CI,* Confidence interval; *HR,* hazard ratio.

outcomes (LS, MALE, and FF-R), and survival outcomes were very significantly worse than those reported 10 years earlier (1999-2004) in the B1 trial. As discussed above, we cannot plausibly argue this is because the CS patients were more comorbid, had anatomically worse baseline disease, or underwent more extensive endovascular interventions. Worse survival may be a consequence of an older patient cohort. However, the claims that newer devices and more familiar practitioners have led to better limb-based outcomes cannot be supported. All of the CS procedures were performed by very experienced interventional radiologists, the immediate technical success rate was good, the immediate complication rate (morbidity and mortality) was low, and the hospital stay was short. It seems very unlikely, therefore, that the long-term results observed in the CS patients are due to suboptimal technical performance of the index procedure. Rather, we believe the most likely explanation is suboptimal patient selection. During the CS study period (2009-2013), only 50 primary FP bypasses were performed for CLTI in our unit.[22] It is probably the case that a significant proportion of the

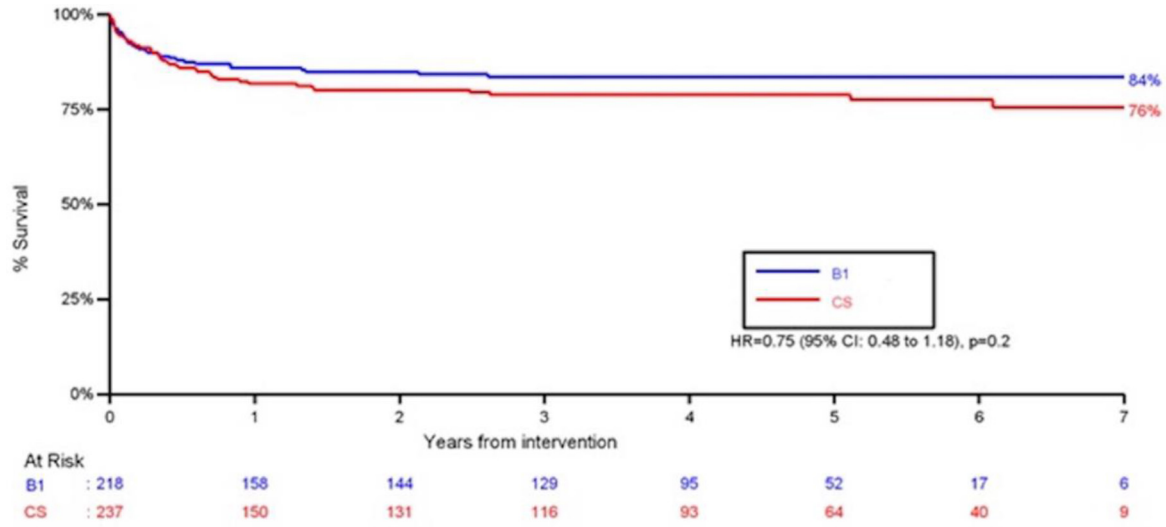

Fig 3. Limb salvage (LS) in contemporary series (*CS*) and BASIL-1 (*B1*) patients undergoing femoropopliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS). *CI,* Confidence interval; *HR,* hazard ratio.

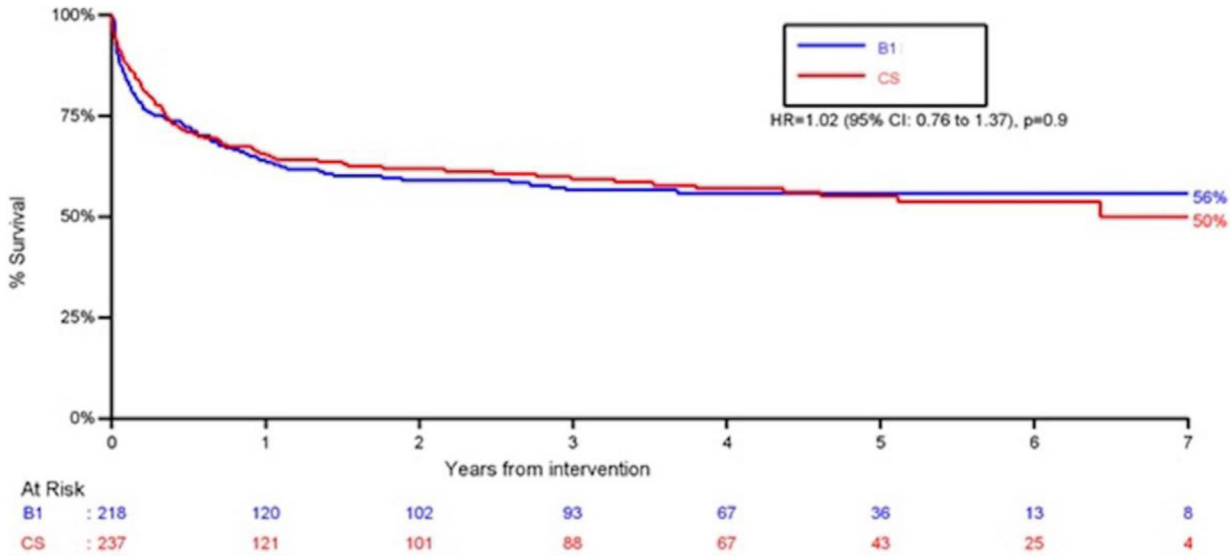

Fig 4. Freedom from major adverse limb events (FF-MALE) in contemporary series (*CS*) and BASIL-1 (*B1*) patients undergoing femoropopliteal plain balloon angioplasty (FP-PBA) with selective bare metal stenting (BMS). *CI,* Confidence interval; *HR,* hazard ratio.

CS patients who underwent PBA ± BMS could and arguably should have had vein bypass, which we know from B1 is associated with better long-term clinical outcomes. In keeping with standard current UK practice, our unit does not routinely use drug-coated balloons (DCBs) or drug-eluting stents (DESs) in de novo peripheral arterial lesions (reserved for in-trial patients or those with in-stent disease); and neither is atherectomy or primary covered stenting part of UK standard of care. There was also probably another group of CS patients who underwent so-called "compassionate" endovascular intervention and whose interests would probably have been best served by primary amputation or conservative treatment.

The results presented here are mirrored by those observed by our group in the IP segment, indicating a consistent effect across the spectrum of lower limb disease treated.[23] Despite the CS having superior technical success, there was no improvement of clinical endpoints for patients with IP disease and CLTI.

In common with most other UK vascular units, patients in our unit who have undergone endovascular revascularization are routinely offered clinical, but not imaging-based, follow-up. Furthermore, not all patients undergo periodic hemodynamic assessment. This was the same in B1. For these reasons, we do not believe lack of routine ultrasound surveillance helps explain the differences observed between the B1 and CS groups.

Although, in the interests of transparency and stimulating debate, we have been quite self-critical of our unit's performance, we must recognize that the study has some limitations. First, we are comparing randomized data with a nonrandomized case series. Second, we do not have comparative Wound, Ischemia, foot Infection (WIfI) scores as this scoring system did not exist at the time the 2 cohorts were treated, and is still not widely used in the UK. And third, we are unable to comment on the possible role of DCBs, DESs, or atherectomy as they were not in use in the UK at the time. That said, the widely held assumption the better short-term patency rates observed with paclitaxel DCBs and DESs in some studies would translate into improved clinical outcomes appears to have been seriously misplaced.[24] Currently, paclitaxel devices are rarely used in the UK outside a research setting; specifically, the BASIL-3 trial. The evidence base supporting the use of atherectomy in CLTI is extremely limited, and, to the best of our knowledge, is not being used in the UK.

In conclusion, the data presented in this study do not support the hypothesis that the increasingly widespread adoption of an endovascular-first strategy to treat CLTI has led to better clinical outcomes. Vein bypass surgery should still be considered the gold-standard treatment. We therefore have to await data from nonindustry-funded randomized controlled trials, such BASIL-2,[25] BASIL-3,[26] and BEST CLI,[27] to establish which patients with CLTI are best served by a primary endovascular intervention and whether in such patients the use of DCBs/DESs is clinically effective and cost-effective, which patients should be offered vein bypass, and which should probably be treated without revascularization. In meantime, the data presented in this paper have led us to question and re-evaluate our revascularization strategies in patients presenting with CLTI.

AUTHOR CONTRIBUTIONS

Conception and design: LM, MP, GB, AB
Analysis and interpretation: LM, GB, SP, AB
Data collection: LM
Writing the article: LM, MP, GB
Critical revision of the article: LM, MP, GB, SP, AB
Final approval of the article: LM, MP, GB, SP, AB
Statistical analysis: SP
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Overall responsibility: AB

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A Comparison of Contemporary Clinical Outcomes Following Femoro-Popliteal Plain Balloon Angioplasty and Bypass Surgery for Chronic Limb Threatening Ischemia

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Abstract

Introduction: Despite the BASIL-1 trial concluding that bypass surgery (BS) was superior to plain balloon angioplasty (PBA) in terms of longer-term amputation free (AFS) and overall survival (OS), CLTI patients are increasingly offered an endovascular-first revascularization strategy. This study investigates whether the results of BASIL-1 are still relevant to current practice by comparing femoro-popliteal (FP) BS with PBA in a series of CLTI patients treated in our unit 10 years after BASIL-1 (1999-2004). **Methods:** We retrospectively analyzed prospectively gathered hospital data pertaining to 279 patients undergoing primary FP BS or PBA for CLTI in the period 2009 to 2014. We report baseline characteristics, 30-day morbidity and mortality, major adverse cardiovascular events (MACE) and long-term AFS, limb salvage (LS), OS, major adverse limb events (MALE), and freedom from re-intervention (FFR). **Results:** 234 (84%) and 45 (16%) patients underwent PBA and BS respectively. PBA patients were significantly older (77 vs 71 years, $P = 0.001$) and more likely to be female (45% vs 28%, $P = 0.026$). Bollinger and GLASS anatomic scores were significantly more severe in the BS group. Technical success was better for BS (100% vs 87%, $P = 0.007$). Index hospital stay was shorter for PBA (9.1 vs 15.6 days, $P = 0.035$) but there was no difference in hospital days or admissions over the next 12 months. AFS (HR 1.00), LS (HR 1.44), OS (HR 0.81), MALE (HR 1.25) and FFR (HR = 1.00) were not significantly different between PBA and BS. **Conclusion:** Important clinical outcomes following FP BS and PBA for CLTI have not changed significantly in our unit in the 10 years following the BASIL-1 trial. BASIL-1 therefore remains relevant to our current practice and should inform our approach to the management of CLTI going forward.

Keywords

peripheral arterial disease, chronic limb threatening ischemia, angioplasty, femoro-popliteal bypass surgery

Introduction

Chronic limb threatening ischemia (CLTI) is an increasing global health and social care problem, mainly due to tobacco use and the increasing worldwide prevalence of diabetes.[1] Despite this, the evidence base informing preferred revascularization strategies in CLTI remains extremely poor.[2] The UK Bypass versus Angioplasty for Severe Ischemia of the Leg trial (BASIL-1) trial remains the only published randomized control trial (RCT) to have compared infra-inguinal bypass surgery (BS) with plain balloon angioplasty (PBA) in patients with chronic limb threatening ischemia (CLTI).[3] BASIL-1 showed that in patients living more than 2 years, a BS first revascularization strategy was associated with better amputation free (AFS) and overall survival (OS).[4] Furthermore, the immediate technical and early clinical failure rate of PBA was higher than with BS, and many patients randomized to PBA had to crossover to BS.[5] BS performed after failed PBA was associated with worse outcomes than primary BS. Furthermore, in an infra-popliteal (IP) BASIL-1 sub-group analysis, BS was associated with better quality of revascularization in terms of relief of ischemia rest pain.[6] So, the only available "level 1" evidence

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strongly suggests that endovascular intervention should normally be reserved for those CLTI patients who cannot have vein BS.[7] Despite this, patients with CLTI are increasingly offered primary endovascular intervention.[8] This non-evidence-based trend is often justified on the grounds that the current results of endovascular treatment are likely to be better than those observed in BASIL-1 in which procedures were performed between 1999 and 2004. This view has to a significant extent been based on the belief that drug coated balloons (DCB) and drug eluting stents (DES) provide superior clinical outcomes when compared to PBA and bare metal stents (BMS); even though there is no evidence for that in the CLTI population, and in fact the opposite appears be true.[9-11] Indeed, there are significant on-going safety concerns associated with the use of paclitaxel DCB and DES[10,11] such that regulatory authorities have felt the need to issue advice regarding their use[12,13] and on-going RCTs evaluating these devices intermittently had their recruitment paused.[14,15] Nevertheless, like many vascular units, we have increasingly used primary endovascular revascularization (in the form of PBA $\pm$ BMS) for CLTI on the grounds that it is assumed to be quicker and easier for patients than BS, at least in the short-term. It is also logistically much easier to deliver timely PBA than it is BS in an increasingly stretched UK National Health Service (NHS). However, a critical internal review of our practice and outcomes suggests that our growing enthusiasm for an endovascular first revascularization strategy where possible in patients presenting with CLTI, based on these considerations, and also a belief that the results of endovascular revascularization have improved since BASIL-1, may have been misguided.[16-18] The aim of the present study, therefore, was to further investigate whether the results of BASIL-1 are still relevant to our current practice by comparing femoro-popliteal (FP) BS with PBA in a series of CLTI patients treated in our unit between 2009 and 2014, 10 years after BASIL-1.

Methods

We retrospectively analyzed prospectively gathered hospital electronic data pertaining to a contemporary series (CS) of patients undergoing FP BS or PBA for CLTI between 1 January 2009 and 31 December 2014, 10 years on from the BASIL-1 recruitment period. Inclusion criteria were the same as for the on-going BASIL-3 trial.[14] In patients undergoing bilateral revascularization during the study period, the first leg undergoing attempted revascularization was designated as the index leg. Patients who had undergone an intervention for CLTI in the index leg within the previous 12 months were excluded. We report baseline characteristics including Bollinger[19] and GLASS[1] anatomic scores, 30-day morbidity and mortality, major adverse cardiovascular events (MACE), and long-term amputation free survival (AFS), limb salvage (LS), overall survival (OS), major adverse limb events (MALE), and freedom from re-intervention (FFR). Major amputation was defined as any above ankle amputation of the index limb. FFR patients were those who did not undergo any subsequent attempted revascularization of the index leg during the study period and did not return to theater for complications. Minor amputation was not considered as a re-intervention as we took the view that this was a likely consequence of the severity of the presenting disease rather than the type of primary revascularization. MALE was defined as any return to theatre for complications, any further attempt at revascularization, or any major amputation during the study period in respect of the index limb. MACE was defined as myocardial infarction (MI), coronary revascularization, transient ischemic attack (TIA), cerebrovascular accident (CVA) or death within 30 days of the primary index revascularization.

Ethical approval was not required for this study as is was deemed as a service outcomes audit.

Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the cohorts were compared using t-test, chi-squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

Results

There were 234 (84%) and 45 (16%) patients who underwent PBA and BS respectively (Table 1). PBA patients were significantly older (77 vs 71 years, $P = 0.00$) and more likely to be female (28% vs 45%, $P = 0.026$). Rates of tissue loss and baseline medical status were similar between the 2 groups. Fewer patients in the PBA group were receiving best medical therapy (BMT) (Table 2). Immediate technical success was better for BS than PBA (100% vs 87%, $P = 0.007$). Index hospital stay was shorter for PBA than BS (9.1 vs 15.6 days, $P = 0.035$). There was no difference in the number of hospital days or admissions out to 12 months, or until primary endpoint. Morbidity and mortality out to 30-days were similar except for MACE, which was lower after BS (2% vs 13.5%, $P = 0.021$) (Table 3). The anatomic extent and severity of arterial disease was significantly worse in the BS as demonstrated by Bollinger and GLASS (Table 4). Out to 7 years AFS (28% vs 29%, HR 0.96, 95% CI 0.64-1.45, $P = 0.8$), LS (76% vs 73%, HR 1.26, 95% CI 0.65-2.44, $P = 0.5$), OS (34% vs 29%, HR 0.81, 95% CI 0.52-1.27, $P = 0.4$), MALE (50% vs 50.0%, HR 1.16, 95% CI 0.71-1.88, $P = 0.6$) and FFR (58% vs 62%, HR = 0.96, 95% CI 0.52-1.77, $P = 0.9$) was not significantly different between the PBA and BS groups (Figures 1–5).

Discussion

Our key conclusion from this study is that important short, medium and long-term clinical outcomes following FP BS and PBA for CLTI in our unit have not changed significantly, in either absolute or relative terms, in the 10 years following the BASIL-1 trial. We believe, therefore, that the results and conclusions of BASIL-1 remain relevant to our current practice and should inform our preferred revascularization strategies for CLTI. Specifically, current and other previously published data

Table 1. A Comparison of Baseline Demographics Between Patients Undergoing Femoro-Popliteal Bypass and Femoro-Popliteal Plain Balloon Angioplasty.

		Plain balloon angioplasty	Bypass surgery	*P* value
		234	45	
Sex	Male	127 (54%)	34 (76%)	0.008
Limb	Right	109 (47%)	27 (60%)	0.1
Age	Mean (sd)	76.9 (11.1)	70.0 (9.9)	0.0001
Indication	Rp	73 (31%)	15 (33%)	<0.0001
	TI	131 (56%)	8 (18%)	
	Both	30 (13%)	22 (49%)	
Immediate technical success	Yes	204 (87%)	45 (100%)	0.007
Hospital days (index admission)	Mean (sd)	9.0 (13.6)	16.4 (21.2)	0.003
Hospital days (to 12 months)	Mean (sd)	23.9 (30.9)	26.0 (27.1)	0.5
Hospital days (to primary end point)	Mean (sd)	39.3 (36.6)	40.4 (33.6)	0.8
Hospital admissions (to primary endpoint)	Mean (sd)	5.1 (4.8)	5.7 (7.1)	0.5
Creatinine	Mean (sd)	107.4 (106.7)	84.0 (36.7)	0.1
Smoker	Never	25 (11%)	8 (18%)	<0.0001
	Ex-smoker	25 (11%)	7 (15%)	
	Current	34 (14%)	22 (49%)	
	Unknown	150 (64%)	8 (18%)	
Diabetes mellitus	Yes	84 (36%)	17 (38%)	0.8
Congestive heart failure	Yes	23 (10%)	6 (13%)	0.4
Hypertension	Yes	151 (65%)	36 (80%)	0.04
Coronary artery disease	Yes	57 (24%)	10 (22%)	0.8
Chronic obstructive pulmonary disease	Yes	27 (12%)	4 (9%)	0.6

Table 2. Medical Therapy at Baseline in Patients Undergoing Femoro-Popliteal Plain Balloon Angioplasty and Bypass Surgery.

Medicine	Specific	Plain balloon angioplasty	Bypass surgery	*P* value
N		234	45	
Statin	Yes	145 (62%)	42(93%)	0.0002
Lipid	Yes	10 (4%)	1 (2%)	0.2
Anti-platelet agent	Yes	162 (65%)	36 (80%)	0.08
Anticoagulation	Yes	29 (12%)	9 (20%)	0.1
ACE inhibitor	Yes	98 (42%)	16 (36%)	0.1
Beta blocker	Yes	55 (24%)	9 (20%)	0.2

Table 3. Morbidity and Mortality (30-days) in Patients Undergoing Femoro-Popliteal Plain Balloon Angioplasty and Bypass Surgery.

		Plain balloon angioplasty	Bypass surgery	*P* value
N		234	45	
MI	Yes	12 (5%)	0 (-)	0.2
TIA/CVA	Yes	14 (6%)	0 (-)	0.1
Surgical intervention	Yes	17 (7%)	4 (9%)	0.8
Amputation	Yes	12 (5%)	3 (7%)	0.7
Mortality (all cause)	Death	9 (4%)	1 (2%)	1.0
Morbidity & mortality (all cause)	Yes	57 (24%)	8 (18%)	0.3
MACE	Yes	32 (14%)	1 (2%)	0.03

do not support the mantra that improvements in endovascular technologies and expertise have translated into better longer-term clinical outcomes for patients with CLTI since patients were randomized in BASIL-1.[6,7,16-18]

Although comparison between RCT data (BASIL-1) and contemporary data are limited we have shown in our previous publications that contemporary clinical outcomes in both PBA and BS in the FP segment are significantly worse now than those observed in BASIL-1. In patients undergoing BS, both survival (HR 1.66, 95%CI 1.00-2.74, $P = 0.05$) and limb-based outcomes (MALE, HR 1.93, 95%CI 1.15-3.22, $P = 0.01$) were significantly worse in the contemporary series.[17] Survival in those undergoing contemporary endovascular intervention was inferior to that observed in BASIL-1 (HR = 0.58, 95% CI: 0.44

Table 4. Bollinger and GLASS at Baseline in Patients Undergoing Femoro-Popliteal Plain Balloon Angioplasty and Bypass Surgery.

		Plain balloon angioplasty	Bypass surgery	*P* value
N		234	45	
Bollinger				
Total Score	Mean (SD)	61 (31.5)	65 (27.2)	0.4
FP Score	Mean (SD)	22 (11.3)	34 (10.8)	<0.0001
IP Score	Mean (SD)	39 (28.2)	32 (23.1)	0.08
GLASS				
FP grade	Median (IQR)	4 (3-4)	4 (4-4)	0.001
0	N	0	1	<0.0001
1	N	13	0	
2	N	29	3	
3	N	60	2	
4	N	132	36	
Missing	N	0	3	
IP grade	Median (IQR)	0 (0 -1)	0 (0-0)	0.2
0	N	164	32	0.0004
1	N	15	7	
2	N	22	3	
3	N	11	0	
4	N	22	0	
Missing	N	0	3	
Run Off Vessels	Median (IQR)	1 (1-2)	1 (1-2)	0.8

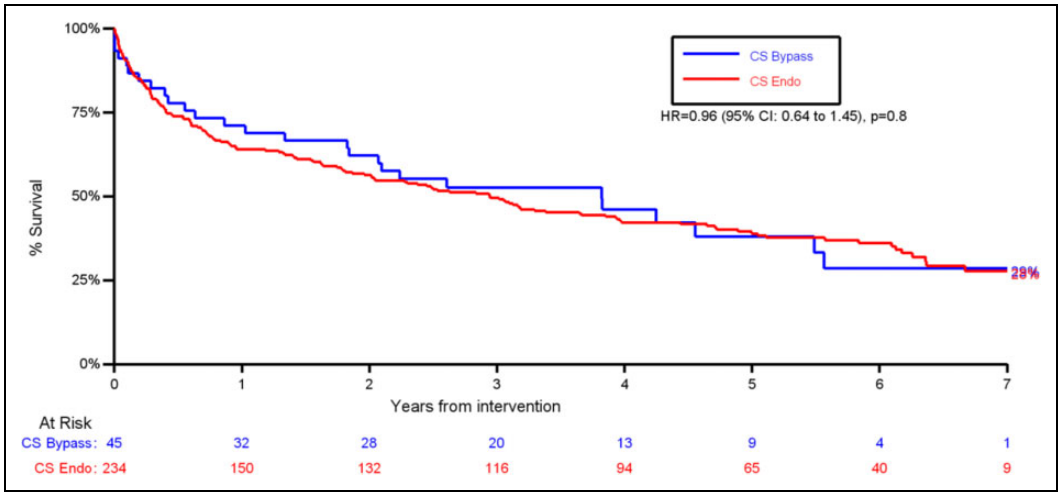

Figure 1. Comparison of amputation free survival following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb-threatening ischemia in a series of patients treated 2009-2014.

to 0.76, $P = 0.0001$) while there was no improvement in limb-based outcomes (MALE, HR = 1.02, 95% CI: 0.76 – 1.37, $P = 0.9$) (unpublished data).

In this study those treated with BS had significantly worse FP Bollinger and GLASS scores, suggesting an increased burden of disease in those patients treated with BS. Interestingly there was not a significant difference in disease burden compared to those treated in BASIL-1. Thus, the severity and complexity of disease treated has not worsened in this time. This supports the hypothesis that in our center only those patients who are deemed very unlikely to have successful endovascular intervention are being considered for BS.

Although out to 7 years clinical outcomes are equivalent, in terms of survival, there seems to be a trend to improved mid-term survival for patients undergoing BS. This may be as a result of more comprehensive use of so-called best medical treatment (BMT) (statin therapy 93% vs 62%, $P = 0.0002$, antiplatelet therapy 80% vs 65%, $P = 0.08$), or the older age of the patients in the PBA group. However, interestingly this trend was not observed when comparing the CS against the B1 cohort.

We must recognize the limitations of this study; the bypass group has small numbers (although reflective of the general spread of interventions in most centers) and may under/over-estimate treatment effect. Single center studies are limited by local practice, expertise and pressure on healthcare resources,

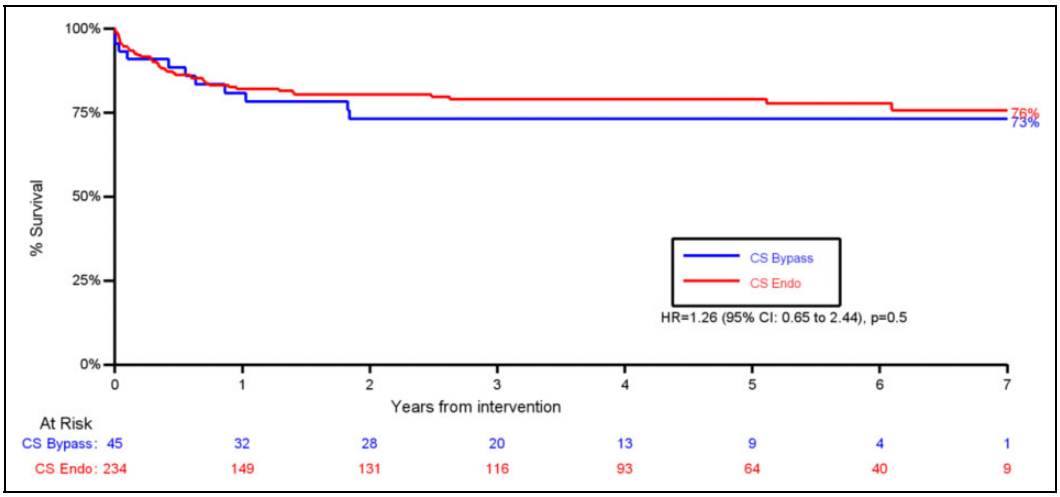

Figure 2. Comparison of limb salvage following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb-threatening ischemia in a series of patients treated 2009-2014.

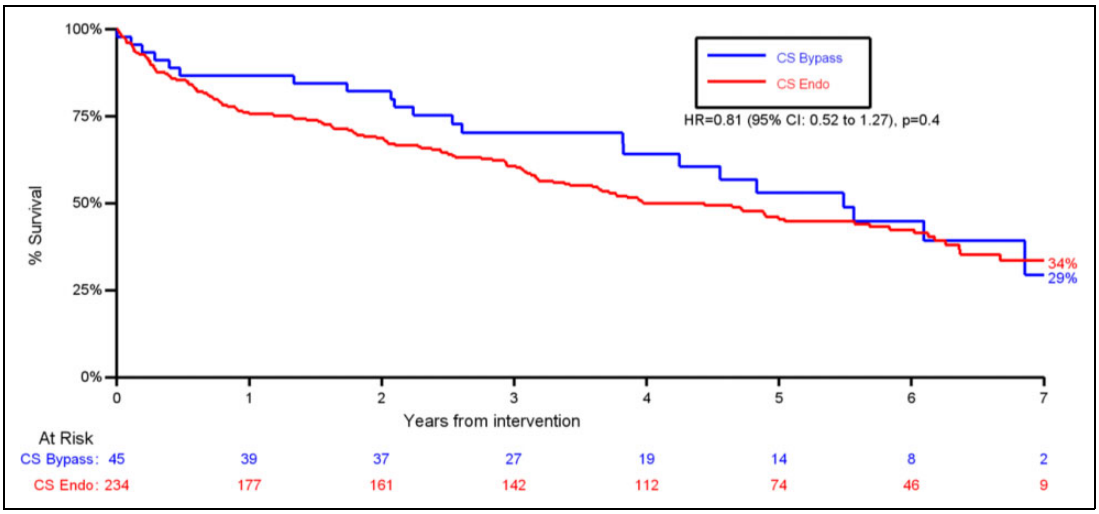

Figure 3. Comparison of overall survival following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb-threatening ischemia in a series of patients treated 2009-2014.

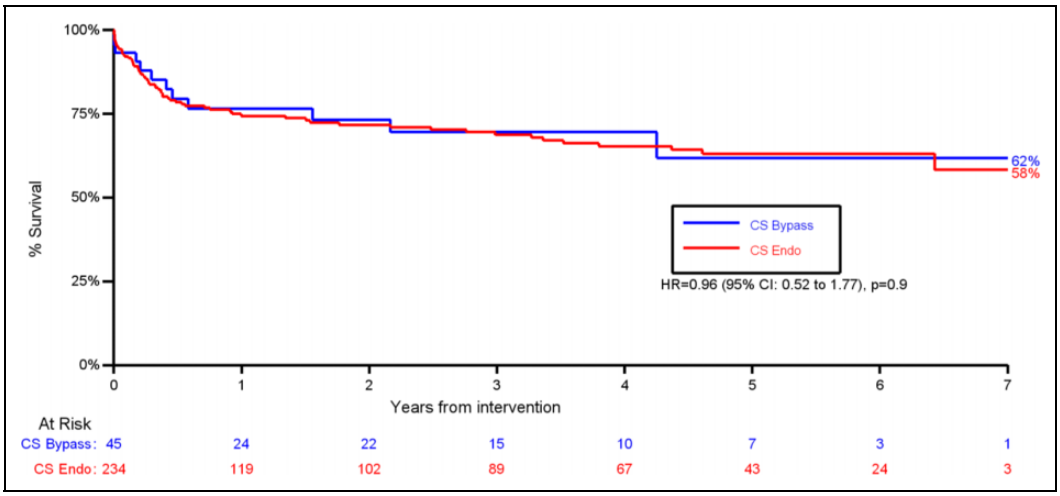

Figure 4. Comparison of freedom from re-intervention following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb-threatening ischemia in a series of patients treated 2009-2014.

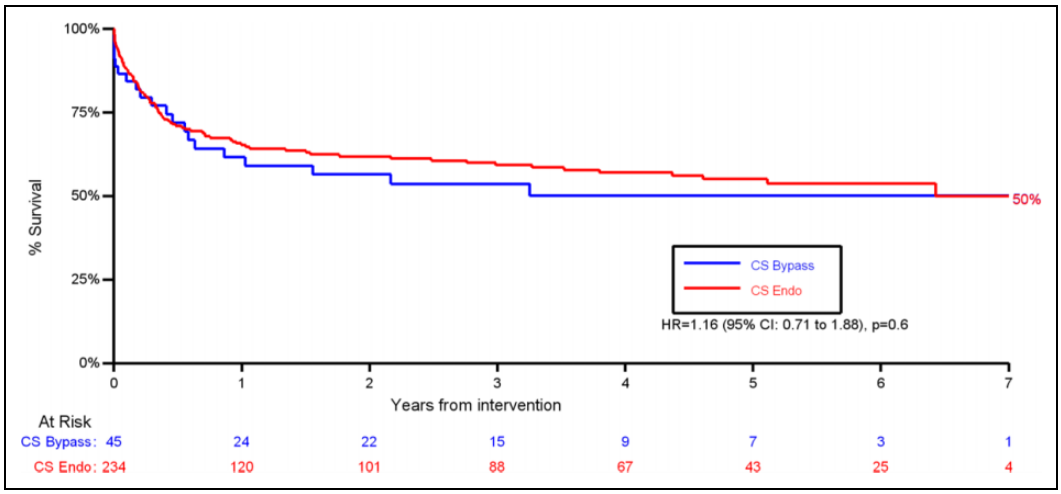

Figure 5. Comparison of major adverse limb events following femoro-popliteal bypass surgery and plain balloon angioplasty for chronic limb-threatening ischemia in a series of patients treated 2009-2014.

questioning generalizability. Finally, the only endo intervention considered here was PBA ± bailout BMS, in many other countries atherectomy and drug eluting devices are used as standard practice and may provide different results (although no independent randomized data supports this as yet).

It seems likely, therefore, that were BASIL-1 to be repeated now, similar results would probably be obtained and conclusions drawn. In other words, what evidence we have suggests that endovascular intervention should still be reserved for those patients who are not suitable for BS either because they do not have an adequate venous conduit or because they have co-morbidities that are thought to preclude open surgery. The clinical superiority of BS over endovascular intervention appears to be especially marked in patients with advanced limb threat[20] as well in those where the target artery path (TAP) is heavily diseased.[21] The results of RCTs such BASIL-2, BASIL-3, and BEST-CLI,[14,22,23] where patients can be stratified by level of limb threat and anatomic severity of disease, are urgently required to improve the evidence base underpinning the management of CLTI. In terms of our own practice, current and other previously published data from our unit have led us to conclude that our revascularization pendulum has swung too far in favor endovascular therapy. Specifically, a 5:1 ratio in favor of PBA versus BS no longer looks appropriate.

Declaration of Conflicting Interests

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Contemporary (2009-2014) clinical outcomes after femoropopliteal bypass surgery for chronic limb threatening ischemia are inferior to those reported in the UK Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial (1999-2004)

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ABSTRACT

Background: Bypass surgery (BS) remains the gold standard revascularization strategy in patients with chronic limb-threatening ischemia (CLTI) owing to infrainguinal disease. The Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial showed that, in patients with CLTI who survived for 2 years or more, BS resulted in better clinical outcomes. Despite this finding, there has been an increasing trend toward an endovascular-first approach to infrainguinal CLTI. Our aim was to investigate whether changes in practice have impacted the clinical outcomes of BS in our unit 10 years after BASIL-1.

Methods: Data for patients who underwent femoropopliteal (FP) BS in BASIL-1 (1999-2004) were retrieved from trial case record forms. The comparator contemporary series (CS) comprised all patients undergoing FP BS for CLTI in our unit between 2009 and 2014. Demographic and clinical outcome data on patients in the CS were collected from the prospectively collected hospital electronic notes. Anatomic patterns of disease in the BASIL-1 and CS cohorts were scored using the Bollinger and GLASS criteria. Statistical analysis was performed in SAS v9.4.

Results: There were 128 patients from BASIL-1 and 50 patients in the CS. Baseline age, gender, affected limb, and diabetes prevalence were similar, as were days spent in hospital out to 12 months and length of follow-up. BASIL-1 patients were more likely to be current smokers ($P = .000$) and had a higher creatinine ($P = .04$). The 30-day morbidity and mortality were higher in BASIL-1 (45.3% vs 22%; $P = .004$). There was no significant difference between BASIL-1 and CS with regard to run-off Bollinger (37.7 vs 32.1; $P = .167$) and IP GLASS (0 vs 0; $P = .390$) scores, with both groups having a median of two runoff vessels. Amputation-free survival (62% vs 28%; hazard ratio [HR], 1.86; 95% confidence interval [CI], 1.18-2.93; $P = .007$), limb salvage (85% vs 69%; HR, 2.31; 95% CI, 1.14-4.68; $P = .02$), overall survival (69% vs 35%; HR, 1.66; 95% CI, 1.00-2.74; $P = .05$) and major adverse limb events (67% vs 47%; HR, 1.93; 95% CI, 1.15-3.22; $P = .01$) were all significantly better in BASIL-1.

Conclusions: Although 30-day mortality and morbidity were significantly lower, all of the examined longer term clinical outcomes after FP BS were significantly worse in the CS group a decade on from BASIL-1. Further research in the form of prospective cohort studies and randomized controlled trials is urgently required to determine if the CS data reported herein are generalizable to current vascular surgical practice and, if so, to determine the reasons for these unexpected outcomes. (J Vasc Surg 2019;69:1840-7.)

Keywords: Peripheral arterial disease; Chronic limb-threatening ischemia; Femoropopliteal bypass

Chronic limb-threatening ischemia (CLTI) is the most severe form of peripheral arterial disease and is characterized by ischemic rest pain and/or tissue loss/gangrene.[1,2] The worldwide incidence of CLTI is increasing owing to aging and the increasing incidence of diabetes mellitus and chronic kidney disease.[3,4] Despite recent advances in medical therapies and endovascular, surgical, and hybrid revascularization technologies and techniques, patients with CLTI remain at high risk of cardiovascular mortality and morbidity, as well as limb loss.[5] With regard to evidence-based revascularization, the first UK National Institute for Health Research Health Technology Assessment-funded Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-1 trial remains the only published randomized controlled trial to have compared a bypass surgery (BS)-first with a plain balloon angioplasty

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(PBA)-first approach to infrainguinal revascularization in CLTI.[6] BASIL-1 showed that, in patients likely to live for more than 2 years, the overall survival (OS) and amputation-free survival (AFS) were better after randomization to BS than to PBA. Despite this Level 1 evidence in favor of BS over PBA, there has been a worldwide trend toward an endovascular-first approach to the treatment of femoropopliteal (FP) disease in patients with CLTI. Those advocating such an approach point to lower periprocedural morbidity and mortality, and further claim that current best endovascular treatment (BET) results in far superior outcomes than those reported in BASIL.[7-9] Although not evidence based, in many vascular units around the world, BS is increasingly reserved for those patients who cannot have endovascular intervention or where such intervention has failed. Owing to the lack of published contemporary series (CS) of BS for CLTI, the impact of such practice on outcomes after BS is unknown. The aim of the present study, therefore, was to compare clinical outcomes after FP BS in a CS (2009-2014) from a single UK academic vascular unit with those reported in the BASIL-1 trial operated a decade earlier (1999-2004).

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cohort study compared with data of patients from the prospective, randomized Bypass versus Angioplasty for Severe Ischaemia of the Leg-1 study
- **Key Findings:** Thirty-day morbidity and mortality were significantly lower and longer term clinical outcomes after femoropopliteal bypass were significantly worse in a contemporary series (2009-2014) of 50 patients with chronic limb-threatening ischemia than results in 128 patients entered in the Bypass versus Angioplasty for Severe Ischaemia of the Leg-1 trial (1999-2004).
- **Take Home Message:** Further research is urgently required to determine if the contemporary series data reported are generalizable to current vascular surgical practice.

METHODS

The BASIL-1 trial randomized 452 patients presenting with CLTI owing to infrainguinal disease to either a BS-first or a PBA-first revascularization strategy. The recruitment period was from 1999 to 2004 and follow-up ended on July 1, 2007.[10] For the present analysis, the BASIL-1 cohort comprised trial patients undergoing primary FP BS with any conduit. The CS cohort comprised patients undergoing primary FP BS for CLTI with any conduit in our unit between 2009 and 2014 and follow-up ended on May 31, 2017. Within the CS study period (2009-2014), 132 FP BS were performed in our unit. Of these, 72 BS were for intermittent claudication (IC) or popliteal aneurysm disease and so were excluded, as were four contralateral BS and six secondary BS performed for failed endovascular interventions within the previous 12 months. This process left 50 patients in the CS cohort undergoing primary FP BS for CLTI compared with 128 BASIL-1 patients.

The BASIL-1 and CS cohorts were compared in terms of baseline factors, 30-day mortality and morbidity, length of hospital stay out to 12 months, AFS, limb salvage, OS, and freedom from reintervention (FFR) and major adverse limb events (MALE). FFR was defined as the absence of subsequent revascularization or intervention for any postoperative complications. Minor amputations were excluded because they were considered a consequence of the clinical presentation. Major amputation was defined as amputation above the ankle joint. Minor amputation includes amputation of single or multiple digits, or transmetatarsal amputation (no Chopart or Lisfranc amputations were performed within the trial). MALE was defined as any ipsilateral limb intervention (excluding minor amputation) after initial intervention. Bollinger[11] and Global Vascular Guideline (GVG) GLASS grade and scores were used to quantify the pattern of anatomic disease before the intervention.

The GLASS score is a new anatomic staging system designed by an expert global panel as part of the GVGs on Chronic Limb Threatening Ischaemia. GLASS is part of the Patient, Limb, Anatomy paradigm presented in the GVG. GLASS involves choosing the target artery pathway for endovascular revascularization from the origin of the SFA (common and deep femoral disease are considered part of inflow and considered corrected before more distal revascularization) to the foot with the aim of establishing inline flow. Disease severity in FP and infrapopliteal (IP) segments are graded separately on features including duration of disease, stenosis or occlusion, and level of calcification. FP and IP grades are combined within a matrix to determine GLASS stage. The GLASS stage is believed likely to correlate with endovascular immediate technical success rates and 12-month limb-based patency. GLASS has been presented at the European Society of Vascular Surgery, Lyon, France in 2017, the Society of Vascular Surgery VAM in San Diego in 2017, and in Boston in 2018. The concept is that GLASS will act as an aid to shared decision making and stratification within trials comparing different forms of revascularization. We understand that the GVG on CLTI are likely to be published in *European Journal of Vascular and Endovascular Surgery* and *Journal of Vascular Surgery* supplement in the second quarter of 2019.

Ethical approval was granted for the BASIL trial (ISRCTN – 45398889). No ethical approval was required for the CS data collection because this analysis is classed as an audit of clinical outcomes.

Table I. Comparison of contemporary series (*CS*) and Bypass versus Angioplasty for Severe Ischaemia of the Leg (*BASIL*) cohorts at baseline

Characteristic	BASIL (n = 128)	CS (n = 50)	*P* value
Conduit			
Vein	89 (70)	39 (78)	.3
Prosthetic	39 (30)	11 (22)	
Distal anastomosis			
Above knee	60 (47)	7 (14)	<.0001
Below knee	68 (53)	43 (86)	
Male sex	78 (61)	36 (72)	.2
Right limb	57 (45)	29 (58)	.1
Age	71 ± 8.1	71 ± 10.1	.8
Indication			
Rest pain	52 (41)	16 (32)	.3
Tissue loss	11 (9)	8 (16)	
Both	62 (48)	26 (52)	
Data missing	3 (2)	0	
Minor amputation			
Yes	30 (23.4)	10 (20)	.6
Smoking status			
Never	17 (13)	8 (16)	**<.0001**
Ex-smoker	65 (51)	23 (46)	
Current	46 (36)	10 (20)	
Unknown	0	9 (18)	
Diabetes mellitus	47 (37)	18 (36)	.9
Congestive heart failure	5 (4)	6 (12)	**.04**
Hypertension	77 (60)	41 (82)	**.006**
Coronary artery disease	35 (27)	10 (20)	.3
Chronic obstructive airway disease	19 (15)	4 (8)	.2
Creatinine	125.6 ± 135.7	85.3 ± 40.2	**.04**
Statin	39 (31)	47 (94)	**<.0001**
Antiplatelet	85 (66)	41 (82)	**.04**
Anticoagulation	9 (7)	10 (20)	**.01**
ACE inhibitor	24 (19)	18 (36)	**.01**
Beta-blocker	13 (10)	10 (20)	**.08**

ACE, Angiotensin-converting enzyme.
Values are presented as number (%) or mean ± standard deviation. Boldface entries indicate statistical significance.

Table II. Comparison of 30-day outcomes in the Bypass versus Angioplasty for Severe Ischaemia of the Leg (*BASIL*) and contemporary series (*CS*) cohorts

Complication	BASIL (n = 128)	CS (n = 50)	*P* value
Mortality (any cause)	7 (5)	1 (2)	.3
Overall morbidity and mortality combined	58 (45)	11 (22)	**.004**
Angina	0	0	–
Myocardial infarction	5 (4)	0	.2
Transient ischemic attack	0	0	–
Cerebrovascular accident	1 (1)	0	.5
Hematoma (not operated)	7 (5)	2 (4)	.7
Hematoma (operated)	2 (2)	1 (2)	.8
Wound infection	37 (29)	6 (12)	**.02**
Lower respiratory tract infection	4 (3)	1 (2)	.7
Upper respiratory tract infection	2 (2)	0	.4
False aneurysm (not operated)	1 (1)	0	.5
False aneurysm (operated)	0	0	–
Any further surgical intervention	3 (2)	4 (8)	.08
Major adverse cardiac event	10 (8)	1 (2)	.1

Values are presented as number (%). Boldface entries indicate statistical significance.

Hazard ratios (HRs) were used to detect statistically important differences in outcomes using 95% confidence intervals (CIs). Differences between the cohorts were compared using the *t*-test, χ^2, and Wilcoxon rank-sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient age, gender, and prevalence of diabetes were similar in both cohorts. Patients in BASIL were more likely to be current smokers, less likely to be on best medical therapy, and had a higher baseline creatinine (Table I). The immediate technical success rate, as judged by the operating surgeon, was very high in both the BASIL-1 (126 of 128 [98%]) and CS (50 of 50 [100%]) cohorts. Minor amputation rates were equivalent between the two cohorts (23.4% vs 20%; $P = .6$), suggesting an equivalent burden of tissue loss. Patients in the BASIL-1 trial had a nonsignificantly longer mean index admission when compared with the patients in the CS cohort (23.2 ± 26.3 days vs 15.6 ± 20.3 days; $P = .7$). However, difference in cumulative inpatient hospital days by 12 months had virtually disappeared (24.2 ± 26.4 days vs 27.3 ± 26.8 days; $P = .5$). Patients in BASIL-1 suffered significantly higher overall combined perioperative (30-day) mortality and morbidity (45% vs 22%; $P = .004$), including higher rates of wound infection ($P = .02$). However, there was no significant difference in major adverse cardiac events (8% vs 2%; $P = .1$; Table II). With regard to long-term clinical outcomes, AFS (62% vs 28%; HR, 1.86; 95% CI, 1.18-2.93; $P = .007$), limb salvage (85% vs 69%; HR, 2.31; 95% CI, 1.14-4.68; $P = .02$), OS (69% vs 35%; HR, 1.66; 95% CI, 1.00-2.74; $P = .05$), and MALE (67% vs 47%; HR, 1.93; 95% CI, 1.15-3.22; $P = .01$) were all significantly better in the BASIL-1 cohort (Figs 1-4). FFR (76% vs 60%; HR, 1.70; 95% CI, 0.88-3.27; $P = .1$) was nonsignificantly better in BASIL-1 when compared with the CS cohort (Fig 5). In terms of anatomic burden of disease, there was no significant difference between the BASIL-1 and CS cohorts with regard to run-off Bollinger score (37.7 vs 32.1; $P = .167$) and IP GLASS grade (0 vs 0; $P = .390$),

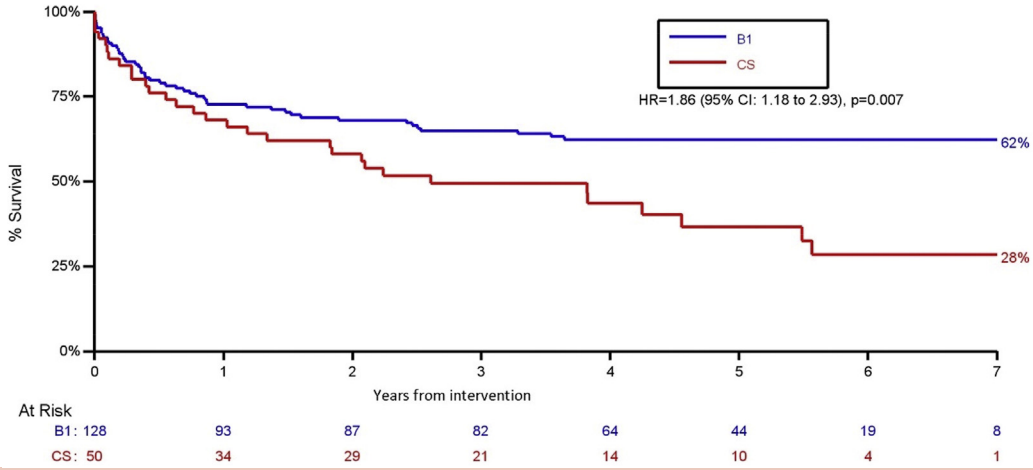

Fig 1. Comparison of amputation-free survival (AFS) in the contemporary series (*CS*) and Bypass versus Angioplasty for Severe Ischaemia of the Leg (*B1*) cohorts. *CI,* Confidence interval; *HR,* hazard ratio.

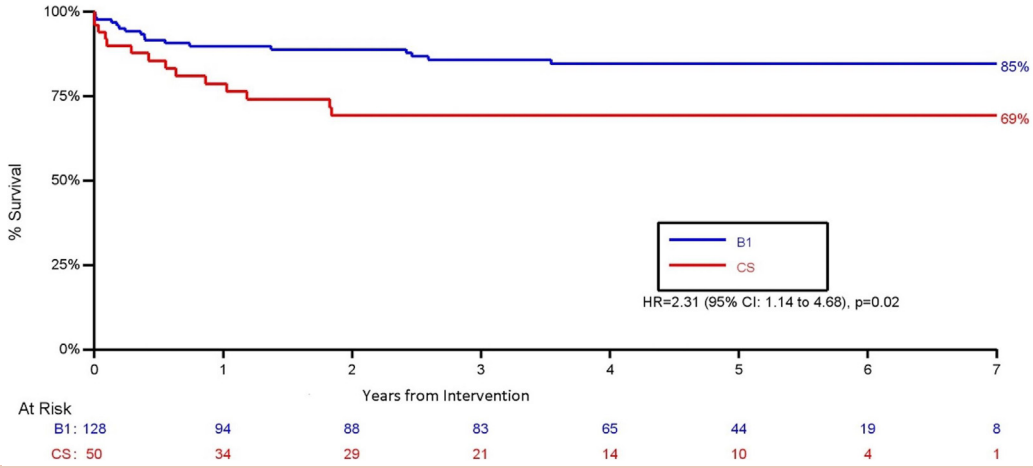

Fig 2. Comparison of limb salvage in the contemporary series (*CS*) and Bypass versus Angioplasty for Severe Ischaemia of the Leg (*B1*) cohorts. *CI,* Confidence interval; *HR,* hazard ratio.

with both groups having a median of two run-off vessels. There was no difference between total Bollinger scores (63.1 vs 65.4; $P = .926$). However, patients in the CS cohort had a significantly higher FP GLASS score (3 vs 4; $P = .000$; Table III).

DISCUSSION

In the present study, although perioperative (30-day) mortality and morbidity were significantly lower, long-term clinical outcomes after primary FP BS for CLTI in our unit between 2009 and 2014 were significantly worse than those reported in the BASIL-1 trial a decade earlier (1999-2004). Further research is required to determine if the CS data reported herein are generalizable to current vascular surgical practice and, if so, to determine the reasons for these unexpected data. Possible causes include a loss of surgical skills as a result of the overall decrease in the number of open vascular procedures and/or a tendency to reserve BS for patients considered unsuitable for endovascular intervention owing the severity of their tissue loss and/or the extent and complexity of their underlying disease.[12-15] Although the loss of surgical skills is certainly possible, this scenario does not seem to be supported by the observation that patients in the CS had lower overall 30-day mortality and morbidity as well as a trend toward a shorter index admission.[16-19] With regard to the clinical severity of disease, the proportion of patients with tissue loss was similar in the two cohorts. We were unable to determine the extent of tissue loss in patients in the CS cohort with the same precision as was the case in BASIL-1. However, using rates of minor amputation as a surrogate, it seems that the severity of tissue loss was broadly similar in both groups. With regard to the anatomic complexity of disease, the Bollinger scoring and GLASS grade suggest a similar disease burden. Importantly, the runoff scores were almost identical for both groups, suggesting that the outflow for BS was equivalent. Postprocedural

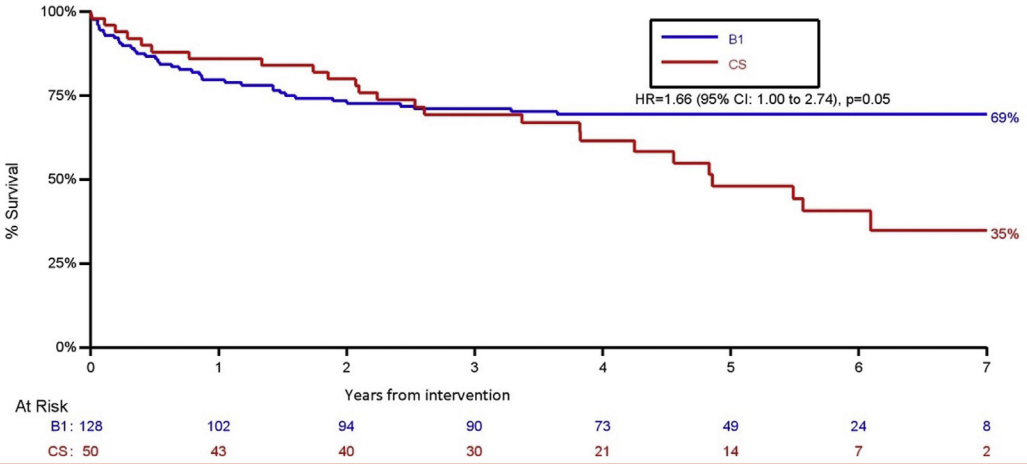

Fig 3. Comparison of overall survival (OS) in the contemporary series (*CS*) and Bypass versus Angioplasty for Severe Ischaemia of the Leg (*B1*) cohorts. *CI,* Confidence interval; *HR,* hazard ratio.

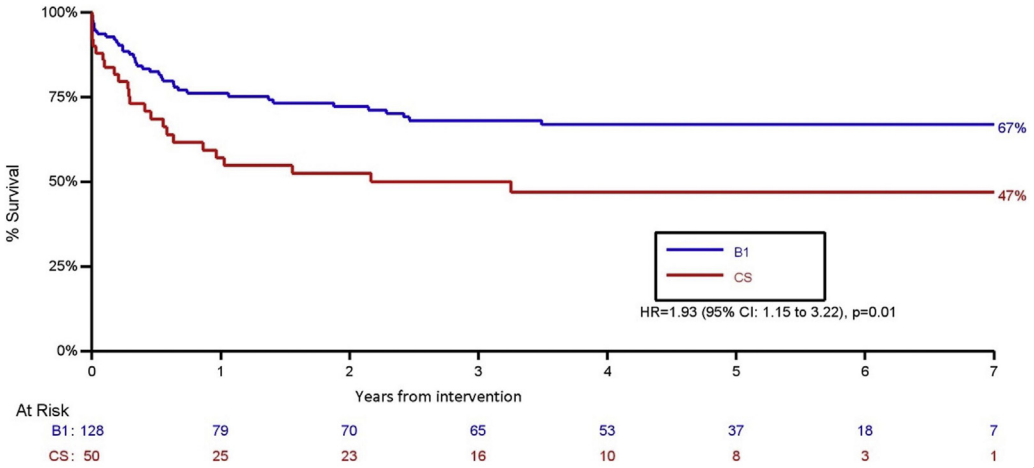

Fig 4. Comparison of major adverse limb event (MALE) in the contemporary series (*CS*) and Bypass versus Angioplasty for Severe Ischaemia of the Leg (*B1*) cohorts. *CI,* Confidence interval; *HR,* hazard ratio.

surveillance may have been different between the two cohorts. Surveillance after bypass was not prescriptive in BASIL-1, its use was not recorded, and reintervention was largely clinically driven. In the CS, only 15 patients were enrolled in formal ultrasound graft surveillance, and none had formal hemodynamic surveillance. As such, it is possible that differences in postbypass care could contribute to the difference in clinical outcomes observed.

An important question is the degree to which our practice and the outcomes reported herein can be generalized more widely to current vascular and endovascular practice within the UK and elsewhere. Like many units, despite a lack of evidence indicating that endovascular intervention offers a more clinically effective and cost-effective option for patients with CLTI who could have a vein bypass, and growing evidence that failed endovascular intervention compromises outcomes after subsequent BS, we have increasingly used an endovascular-first approach to the management of CLTI. Thus, during the study period (2009-2014), almost five times more (n = 237) patients had a FP endovascular intervention for CLTI than had BS (n = 50). In the UK, virtually all patients with CLTI are managed within the National Health Service, where care is provided free at the point of delivery to all UK and European Union citizens by salaried vascular surgeons and interventional radiologists. As such, the turf battles and reimbursement issues seen elsewhere in the world are largely irrelevant to UK practice. Rather, the main reason for our endovascular preference is probably a reluctance to subject elderly and comorbid patients to a prolonged surgery and, linked to that, a belief that an endovascular approach is associated with less resource use in terms of operating theatre time and bed days in hospital. However, these beliefs are not supported by hard data and we have to accept that our current practice

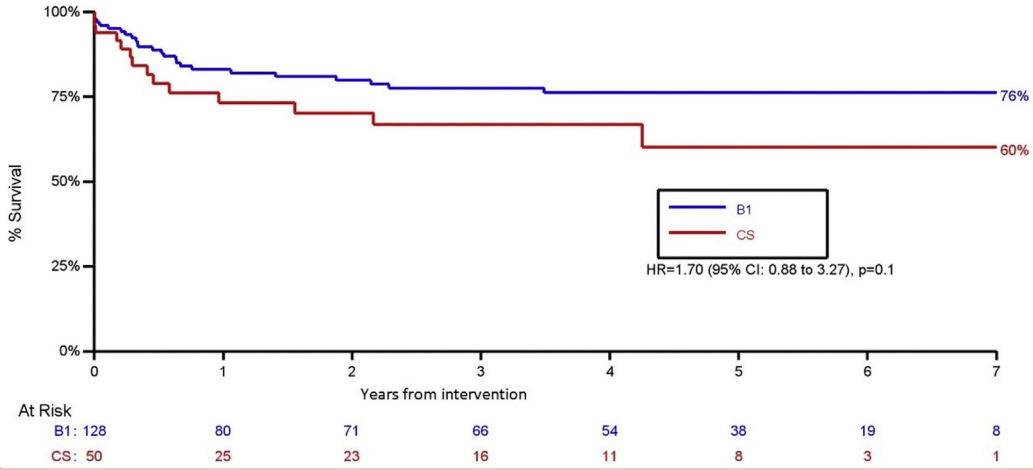

Fig 5. Comparison of freedom from reintervention (FFR) in the contemporary series (*CS*) and Bypass versus Angioplasty for Severe Ischaemia of the Leg (*BI*)cohorts. *CI,* Confidence interval; *HR,* hazard ratio.

Table III. A comparison of anatomic disease using Bollinger score between the Bypass versus Angioplasty for Severe Ischaemia of the Leg (*BASIL*) and contemporary series (*CS*) cohorts

	BASIL	CS	*P* value
Total Bollinger score	63.1 ± 23.4	65.4 ± 28.5	.926
Total runoff Bollinger score (above knee bypass)	40.8 ± 25.1	27.1 ± 27.5	.189
Total runoff Bollinger score (below knee bypass)	35.0 ± 18.5	33 ± 22.6	.623
Total runoff Bollinger score (combined)	37.7 ± 21.9	32.1 ± 23.1	.167
No. of runoff vessels	2 (1-2)	2 (1-3)	.051
FP GLASS	3 (2-4)	4 (4-4)	.000
IP GLASS	0 (0-0)	0 (0-0)	.390
Possible target artery			
AT (N)	48	26	.105
PT (N)	34	21	.083
PP (N)	66	25	.544

AT, Anterior tibial artery; *FP,* femoropopliteal; *IP,* infrapopliteal; *PP,* peroneal artery; *PT,* posterior tibial artery.
Values are presented as mean ± standard deviation, median (interquartile range), or number.

may not be maximizing long-term clinical outcomes for the greatest number of our patients with CLTI.

Interestingly, in the UK, Heikkila et al[20] have recently published 1-year outcomes after lower limb revascularization using data from the National Vascular Registry, Hospital Episode Statistics, and the Office of National Statistics. The authors conclude that OS and amputation rates have improved significantly over a 10-year period. They suggest that one reason for the observed improvement may be a centralization of services owing to increased specialization in vascular surgery. These UK national data would seem to starkly contradict those reported herein from a single UK academic vascular unit. However, it must be noted that Heikkila et al grouped together a wide range of surgical and endovascular procedures, studies patients with CLTI and IC, and that their follow-up was short. Unfortunately, at the present time, there are very few other published data with which we can compare our own long-term outcome data. Most surgical and endovascular CLTI cohorts reported in the literature have limited follow-up and/or mix CLTI with IC and/or mix FP with IP procedures, which makes interpretation of the data extremely difficult.[21-23]

Therefore, there is a clear and urgent need to perform further randomized controlled trials to determine the pros and cons of a BET-first vs a BS-first revascularization strategy in subgroups of patients with CLTI presenting with different degrees of tissue loss and anatomic complexities of disease. To this end, in the UK, the National Institute for Health Research Health Technology Assessment is funding the BASIL-2[24] and BASIL-3[25] studies to inform practice in IP disease and the impact of drug-eluting technologies in the FP segment, respectively. In the United States, the National Institutes of Health have funded the BEST-CLI[26] trial. Together, these

ongoing trials will report contemporary clinical outcomes in several thousand patients undergoing BET and BS for CLTI and inform evidence-based revascularization decisions going forward.

CONCLUSIONS

Although 30-day mortality and morbidity were significantly lower, all of the examined longer-term clinical outcomes after FP BS were significantly worse in the CS group a decade on from BASIL-1.

AUTHOR CONTRIBUTIONS

Conception and design: LM, MP, GB, AB
Analysis and interpretation: LM, SP
Data collection: LM
Writing the article: LM
Critical revision of the article: LM, MP, GB, SP, AB
Final approval of the article: LM, MP, GB, SP, AB
Statistical analysis: SP
Obtained funding: Not applicable
Overall responsibility: AB

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Evaluation of the Global Limb Anatomic Staging System in patients with chronic limb-threatening ischemia undergoing endovascular intervention for femoropopliteal disease

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ABSTRACT

Background: The Global Limb Anatomic Staging System (GLASS) is a new method of quantifying the anatomic severity of infrainguinal disease in patients with chronic limb-threatening ischemia. However, because GLASS has undergone limited validation, its value as an aid to shared decision-making regarding the choice of revascularization strategy remains incompletely defined. Here we report the relationship between GLASS and outcomes in a contemporary series comprising all 309 patients who underwent an attempt at femoropopliteal and/or infrapopiteal endovascular therapy for chronic limb-threatening ischemia in our unit between 2009 and 2014.

Methods: Baseline patient characteristics and outcome data including immediate technical success (ITS), amputation-free survival (AFS), overall survival, limb salvage, freedom from reintervention (FF-R), and freedom from major adverse limb events (FF-MALE) were obtained from hospital databases. GLASS grades and stage were obtained from pre-endovascular therapy angiographic imaging. Outcome data were censored on May 31, 2017.

Results: Baseline patient characteristics were similar across different GLASS femoropopliteal and IP grades and overall limb stages. Worsening GLASS stage was associated with a significant reduction in ITS (97.5% vs 91.5% vs 84.0%; $P = .029$). At 72 months FF-R (hazard ratio, 2.00; 95% confidence interval, 1.11-3.57; $P = .020$) and FF-MALE (hazard ratio, 1.76, 95% confidence interval, 1.10-2.81; $P = .019$) were significant worse in GLASS stage 3 than in stage 2 limbs.

Conclusions: In our study, there were significant differences in ITS, FF-R and FF-MALE between limbs with GLASS stage 2 and 3 disease. However, further GLASS refinement seems likely to be required if its usefulness in everyday clinical practice as an aid to shared decision-making regarding the choice of revascularization strategy is to be maximized. (J Vasc Surg 2023;77:474-9.)

Keywords: Peripheral arterial disease; Chronic limb-threatening ischemia; Angioplasty; Femoropopliteal bypass surgery; Global anatomic staging system

The Global Vascular Guidelines (GVG) were published in June 2019 with the aim of promoting an evidence-based approach to the management of patients with chronic limb-threatening ischemia (CLTI) across the world.[1,2] The GVG proposed the Global Limb Anatomic Staging System (GLASS) as a new method for assessing the anatomic extent and complexity of infrainguinal disease based on the evaluation of angiograms. The GLASS process begins by identifying a target artery path (TAP), which represents the route of endovascular therapy (EVT) considered most likely to provide continuous inline flow to the foot. Below the knee, unless angiosome-based revascularization is being attempted, the TAP will usually include the least diseased crural artery. GLASS begins at the superficial femoral artery origin as the common and deep femoral arteries are considered inflow vessels. Femoropopliteal (FP) and infrapopliteal (IP) segments are considered separately and graded from 1 (least severe) to 4 (most severe). Severe calcification increases the FP/IP segment grade by 1. There is also a pedal modifier based on the status of the pedal arch. FP and IP grades are combined to provide a GLASS stage I (least severe) to III (most severe) for the whole limb. GLASS stages are designed to correspond with low, intermediate, and high complexity EVT cases. The intention is that GLASS will act as an aid to shared decision-making regarding choice of revascularization strategy by helping to predict immediate

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technical success (ITS) and 1-year limb-based patency (LBP) of the TAP after EVT. Our first attempt at GLASS evaluation was based on angiograms and outcome data from the UK National Institute of Health Research Health Technology Assessment-funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) trial.[3,4] We concluded that the GLASS score was useful in predicting medium to long term limb-based outcomes in patients undergoing EVT, but not bypass surgery. However, because BASIL-1 patients were treated between 1999 and 2004, it has been suggested that, given the more recent advances in endovascular technologies and techniques, the relationships between GLASS and outcomes after EVT may have changed. In response to this suggestion, we now report the relationship between GLASS and clinical outcomes in a prospectively documented, contemporary series of all patients undergoing an attempt at FP EVT for CLTI in our unit between January 1, 2009, and December 31, 2014, which is 10 years later than the BASIL-1 recruitment period.[5]

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cohort study
- **Key Findings:** Worsening GLASS stage had a significant reduction in immediate technical success (97.5% vs 91.5% vs 84%). In the long term, those with GLASS stage 3 limbs had worse freedom from reintervention (HR, 2.0) and major adverse limb events (HR, 1.76) than those with GLASS stage 2 limbs.
- **Take Home Message:** GLASS has the potential to be a valuable tool in predicting likely technical and clinical success of endovascular treatment in patients with infra-inguinal arterial disease causing CLTI.

METHODS

The present study includes 309 consecutive patients with CLTI who underwent a primary attempt at FP and/or IP EVT as their first revascularization procedure in a single vascular unit between January 1, 2009, and December 31, 2014. Only patients' primary intervention was included for analysis, repeat interventions on the treatment leg were defined as a reintervention; contralateral limb interventions were excluded. Baseline patient and clinical outcome data (ITS, amputation free survival [AFS], overall survival [OS], limb salvage [LS], freedom from reintervention [FF-R], and freedom from major adverse limb events [FF-MALE]) were obtained from prospectively gathered hospital records and databases. Outcome data were censored on May 31, 2017. ITS was recorded contemporaneously at the time of the EVT by the senior responsible interventionalist based on successful device use and satisfactory postintervention angiographic appearances. Those patients where the intervention was not immediately successful were still included for the analysis of clinical outcomes. AFS is the time to major (above ankle) amputation or to death from any case, whichever occurs first. OS is the time to death from any cause. LS is absence of major limb amputation FF-R is the absence of an attempt at further revascularization of the index limb or of intervention relating to complications of the primary procedure. Minor amputations (distal to the ankle) were not considered a reintervention because they are were considered more likely to be a consequence of the severity of the presenting clinical condition than the success of EVT. FF-MALE is the absence of any attempt at a further revascularization, or a major amputation, of the index limb. MALE survival (MALE-S) is survival without MALE. LBP is a composite end point based on radiological loss of patency, reintervention, or significant decrease in the ankle brachial pressure index (>0.15). We were unable to calculate LBP because, in the UK, routine postintervention imaging and hemodynamic surveillance of patients with CLTI undergoing EVT is not standard of care. We, therefore, report 12-month FF-R and FF-MALE instead. Pre-EVT digital subtraction angiograms were GLASS assessed according to GVG instructions. The TAP was agreed by two assessors (LM and MP) and differences were settled with discussion; in those undergoing IP intervention, the TAP was defined as the tibial vessel that underwent intervention. FP and IP segments were graded independently along with degree of calcification and combined to provide a GLASS stage for the overall limb. The pedal modifier was not used because foot views were not available for all patients. All patients had undergone evaluation and, where necessary, endovascular and/or surgical correction of inflow disease before the index infrainguinal EVT. Ethical committee approval was not required owing to the retrospective design of this study, the study was registered with the institutional audit department. Differences in baseline patient characteristics between GLASS stages of disease were compared using the t test, χ^2 test, Fisher's exact test, and Wilcoxon rank-sum test according to distribution of data. Hazard ratios (HRs) were used to detect statistically important differences in clinical outcomes using 95% confidence intervals (CIs). Statistical analysis was performed using SPSS v 24 (SPSS, Inc, Armonk, NY).

RESULTS

Baseline patient characteristics were similar between different GLASS grades and stages (Table I). Increasing GLASS stage was associated with increasing age and those with FP grade 1 had significantly higher baseline creatinine. GLASS grades and stages and characteristics EVT are shown in Tables II and III. There was no significant difference between the EVT performed and GLASS stage. There was a significant difference in the length of the index admission between GLASS stages (8.4 days vs 12.6 days vs 8.2 days; $P = .038$), but total days in hospital was not different out to 12 months (29.0 days vs 23.4 days vs 23.1 days; $P = .516$). ITS decreased significantly with increasing GLASS stage (I, 97.5% vs II, 91.5% vs III, 84.0%;

Table I. Baseline demographics of patients by Global Limb Anatomic Staging System (*GLASS*) stage

	G1	G2	G3	Total	*P* value
Number	40 (12.9)	82 (26.5)	187 (60.5)	309	
Male sex	22 (55)	38 (46.3)	90 (48.1)	150 (48.5)	.657
Limb (left)	21 (52.5)	48 (58.5)	105 (56.1)	174 (56.3)	.817
Age, years	72.2	75.9	78.0	76.7	**.006**
Rest pain	9	19	62	90	.111
Tissue loss	27	52	92	171	
Rest pain and tissue loss	4	11	33	48	
Stent	3	1	20	24	.028
ITS	39 (97.5)	75 (91.5)	157 (84.0)	271 (87.7)	**.029**
Index IP hospital days	8.4	12.6	8.2	9.4	**.038**
12-Month hospital days	29.0	23.4	23.1	23.9	.516
Never smoked	1	9	20	30	.063
Ex-smoker	6	6	38	50	
Current smoker	7	16	21	44	
Unknown	26	51	108	185	
DM	21	33	74	128 (41.4)	.311
CHF	4	9	11	24	.295
HTN	26	53	133	212 (68.6)	.499
CAD	9	22	51	82 (26.5)	.823
COPD	5	12	18	35 (11.3)	.476
Creatinine (mmol/L)	128.6	126.1	97.6	109.2	**.034**
Statin	24	50	123	197 (63.8)	.428
Antiplatelet	21	37	99	157 (50.1)	.272
Anticoagulation	10	22	52	84 (27.2)	.459
ACE	14	27	63	104 (33.7)	.466
β-Blocker	11	18	48	77 (24.9)	.428

ACE, Angiotensin-converting enzyme; *CAD*, coronary artery disease; *CHF*, Congestive Heart Failure; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *G1*, GLASS stage 1; *G2*, GLASS stage 2; *G3*, GLASS stage 3; *HTN*, hypertension; *IP*, infrapopliteal grade; *ITS*, immediate technical success.
Values are number or number (%).
Boldface entries indicate statistical significance.

Table II. Distribution of femoropopliteal (*FP*) grade and infrapopliteal (*IP*) grade and numbers per Global Limb Anatomic Staging System (GLASS) stage

	FP 0	FP 1	FP 2	FP 3	FP 4
IP 0	0	6	20	45	95
IP 1	3	4	3	2	10
IP 2	7	2	9	9	19
IP 3	5	3	4	4	12
IP 4	6	2	4	8	27

GLASS Stage 1.
GLASS Stage 2.
GLASS Stage 3.

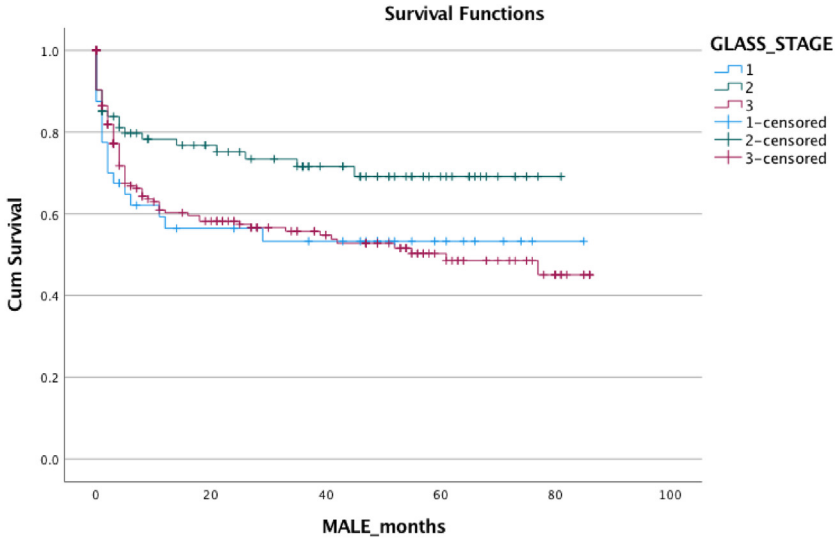
Table III. Distribution of arterial segments treated by Global Limb Anatomic Staging System (GLASS) stage

Arteries treated	G1	G2	G3	Total
SFA	23	38	60	121
POP	0	9	32	41
SFA + POP	3	12	33	48
SFA + POP + Crural	3	6	19	28
SFA + Crural	2	3	9	14
POP + Crural	1	5	25	31
Crural	8	9	9	26
Total	40	82	187	309

Crural, Anterior tibial or tibioperoneal trunk or posterior tibial or peroneal; *POP*, popliteal artery; *SFA*, superficial femoral artery.

$P = .029$) and were concordant with those set out as expected in the GVG.

There was no significant difference between GLASS stage and 12-month FF-R (73%, 89%, and 72%; $P = .419$) or FF-MALE (59%, 78%, and 61%; $P = .566$). There was no significant relationship between GLASS stage and long-term AFS (38.6% vs 30.2% vs 36.9%; $P = .710$), OS (45.5% vs 28.8% vs 40.8%; $P = .695$), LS (73.7% vs 84.9%



*numbers at risk

GLASS	12 M	24 M	36 M	48 M	60 M	72 M
1	20	18	17	13	7	3
2	52	44	34	25	14	6
3	89	75	60	48	29	18

Fig 1. Major adverse limb events (*MALE*) by Global Limb Anatomic Staging System (*GLASS*) stage. *Cum*, cumulative.

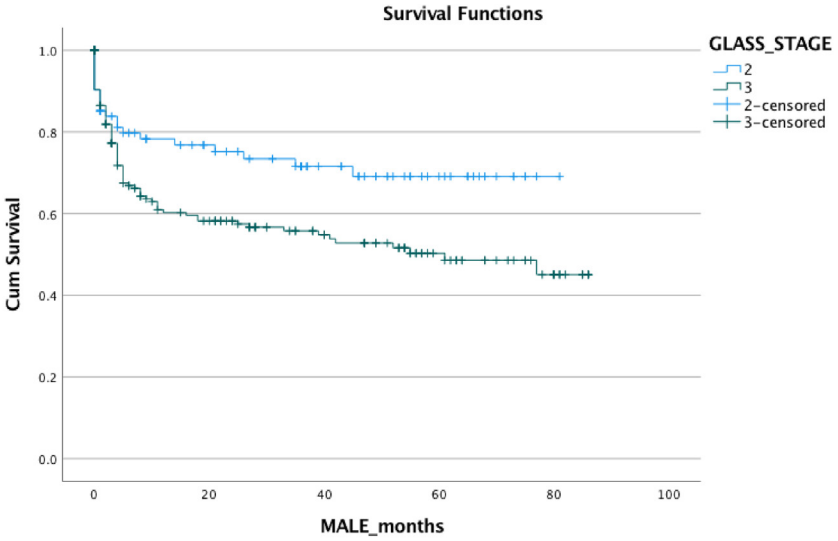
vs 74.7%; $P = .771$), FF-MALE (53.3% vs 69.1% vs 48.6%; $P = .376$), FF-R (68.6% vs 77.9% vs 55.4%; $P = .172$), or MALE-S (29.2% vs 16.4% vs 20.5%; $P = .342$) (Fig 1). However, the 12-month (HR, 1.83; 95% CI, 1.07-3.12; $P = .026$) and 24-month (HR, 1.71; 95% CI, 1.03-2.84; $P = .039$) FF-MALE, and 12-month FF-R (HR, 2.31; 95% CI, 1.13-4.71; $P = .022$) were significantly worse in limbs with GLASS stage III disease (Figs 2 and 3).

Out to 72 months of follow-up, AFS (HR, 0.95; 95% CI, 0.67-1.35; $P = .780$), OS (HR, 0.76; 95% CI, 0.55-1.06; $P = .107$), LS (HR, 1.57; 95% CI, 0.78-3.16; $P = .207$), and MALE-S (HR, 1.16; 95% CI, 0.86-1.55; $P = .332$) were not significantly different between GLASS stage II and III disease. However, FF-MALE (HR, 1.76; 95% CI, 1.10-2.81; $P = .019$) FF-R (HR, 2.00; 95% CI, 1.11-3.57; $P = .020$) remained significantly worse for GLASS stage III disease in the long term.

There was no significant relationship between FP grade and 12-month FF-R and FF-MALE, or long term AFS ($P = .610$), OS ($P = .180$), LS ($P = .528$), FF-R ($P = .229$), FF-MALE ($P = .834$), and MALE-S ($P = .923$). There was no significant relationship between IP grade, 12-month FF-R and FF-MALE, or long-term AFS ($P = .061$), OS ($P = .570$), LS ($P = .214$), FF-R ($P = .980$), FF-MALE ($P = .311$) and MALE-S ($P = .122$) (Supplementary Table and Figs 1 and 2, online only). Using FF-MALE as a surrogate for LBP, observed outcomes are broadly similar to those set out as expected in the GVG (stage II 78% vs 50%-70%; stage III 61% vs <50%).

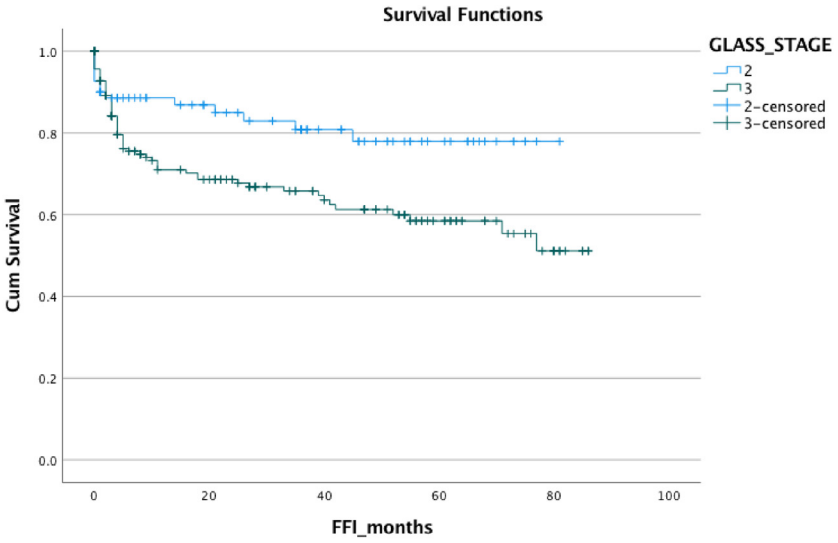
DISCUSSION

The GVG recommends a Patient risk, Limb severity, and Anatomic (PLAN) approach to CLTI management. This practice emphasizes the importance of considering patient fitness and limb threat (using Wound, Ischemia, and foot Infection [WIfI][6]) alongside the anatomic disease severity when embarking on shared decision-making regarding infrainguinal revascularization.[7-9] Regarding anatomy, GVG proposes GLASS as a method of predicting ITS and 12-month LBP in patients being considered for EVT. In our study, we found ITS significantly decreases with advancing GLASS stage, although ITS was somewhat better than that set out in GVG.[10] Regarding FF-MALE and FF-R, GLASS stage III limbs had significantly worse outcomes than GLASS II limbs at 12, 24, and 72 months. Surprisingly, GLASS I limbs had outcomes similar to those with GLASS III disease. However, there were relatively few GLASS I limbs and we did not have WIfI data. So, unexpectedly poor outcomes in these limbs may be explained by limb threat owing to wounds and/or infection rather than ischemia. The pedal modifier was not calculated in this cohort, owing to inconsistency in the availability and quality of



GLASS	12 M	24 M	36 M	48 M	60 M	72 M
2	52	44	34	25	14	6
3	89	75	60	48	29	18

Fig 2. A comparison of major adverse limb events (*MALE*) between Global Limb Anatomic Staging System (*GLASS*) stage 2 and 3 disease. *Cum*, cumulative.



GLASS	12 M	24 M	36 M	48 M	60 M	72 M
2	51	43	33	24	14	6
3	91	77	62	49	30	17

Fig 3. A comparison of freedom from reintervention (*FFI*) between Global Limb Anatomic Staging System (*GLASS*) stage 2 and 3 disease. *Cum*, cumulative.

the angiograms; it is conceivable that pedal disease is the main contributor in GLASS I patients suffering with CLTI.[11] Although GLASS was proposed as a means of predicting 12-month LBP, for reasons discussed, we substituted 12-month FF-MALE and FF-R. However, these end points mainly depend on symptom recurrence and may miss patients with asymptomatic, or mildly symptomatic, treatment failures that would be captured by LBP based on hemodynamic testing and surveillance imaging. Before GLASS, the Inter-Society Consensus for the

Management of Peripheral Arterial Disease (TASC) II was the most used tool for reporting on the disease severity. However, despite some correlation between limb-based outcomes and TASC II, it has not been adopted into everyday practice.[12-14] GVG authors hope GLASS based on grading and staging the EVT TAP will represent a significant advance and be used more widely. However, the authors recognize that, without further validation and probably further refinement, GLASS cannot currently be used independently to assess the appropriateness of EVT for individual patients.

Limitations of this study include its retrospective single-center design, lack of a WIfI score, the inability to calculate the pedal modifier, and the inability to specifically calculate LBP. Nevertheless, the authors have provided alternative data where possible to inform the reader of the degree of limb threat and the success of EVT.

In summary, our study suggests that GLASS, when considered alongside patient fitness and limb threat, is likely to help predict ITS and 12-month limb-based outcomes in patients with CLTI being considered for EVT. However, further refinement, particularly with respect to stage I disease in the context of different WIfI scores, is probably required. To that end, we are prospectively gathering GLASS and WIfI data within the UK BASIL-2 and BASIL-3 trials, which are expected to report in 2022 and 2023, respectively.

AUTHOR CONTRIBUTIONS

Conception and design: LM, GB, AK, MC, AWB
Analysis and interpretation: LM, HOBD, AWB
Data collection: LM, MP, GB
Writing the article: LM, MP, HOBD, AWB
Critical revision of the article: LM, MP, GB, HOBD, AK, MC, AWB
Final approval of the article: LM, MP, GB, HOBD, AK, MC, AWB
Statistical analysis: LM
Obtained funding: Not applicable
Overall responsibility: LM

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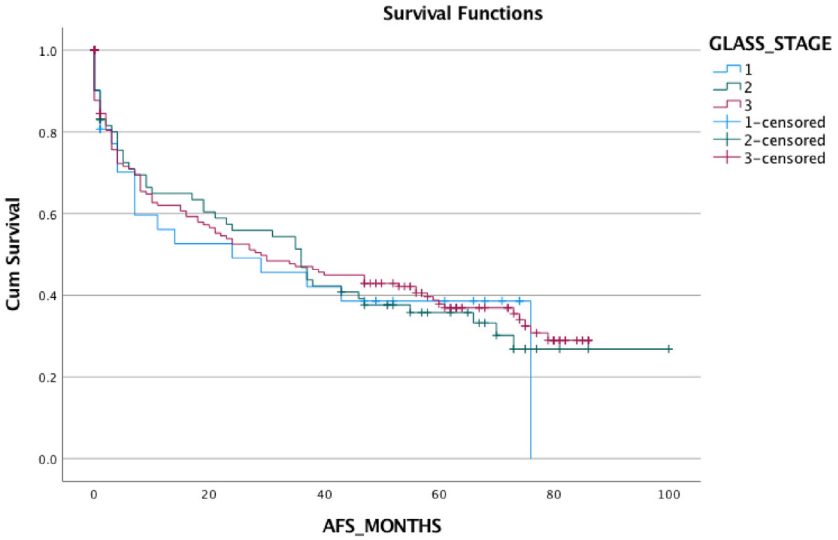
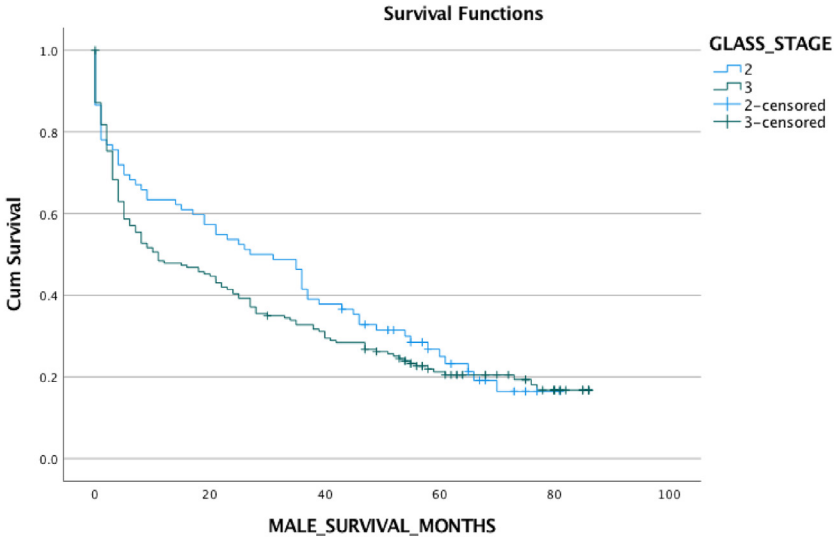


*numbers at risk

GLASS	12 M	24 M	36 M	48 M	60 M	72 M
1	16	14	13	10	7	3
2	43	37	31	23	16	9
3	91	77	69	60	40	26

Supplementary Fig 1 (online only). Amputation-free survival (*AFS*) by Global Limb Anatomic Staging System (*GLASS*) stage. *Cum*, cumulative.



GLASS	12 M	24 M	36 M	48 M	60 M	72 M
1	20	18	17	13	7	3
2	52	44	40	25	14	6
3	89	75	60	48	29	18

Supplementary Fig 2 (online only). A comparison of major adverse limb events (*MALE*) survival between Global Limb Anatomic Staging System (*GLASS*) stage 2 and 3 disease. *Cum*, cumulative.

Supplementary Table (online only). The 72-month clinical outcomes by Global Limb Anatomic Staging System (GLASS) stages 1, 2, and 3

	G1	G2	G3	*P* value
AFS	39	30	37	.711
LS	76	85	75	.772
FF-R	69	78	55	.159
FF-MALE	53	69	49	.369
OS	46	29	41	.695
MALE-S	29	16	21	0.337

AFS, Amputation-free survival; *FF-R*, freedom from reintervention; *FF-MALE*, freedom from major adverse limb events; *OS*, overall survival; *MALE-S*, survival without major adverse limb events.
Values are percent.